Medication Appropriateness and Regimen Complexity in Chronic Kidney Disease

by

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A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

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DECLARATION OF ORIGINALITY

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STATEMENT OF ETHICAL CONDUCT

The research associated with this thesis abides by the Australian codes on human and animal experimentation, the guidelines by the Australian National Ethics and Institutional Biosafety Committees of the University. All research involving patients with chronic kidney disease was conducted under the approval of the Tasmanian Health and Medical Human Research Ethics Committee (Approval numbers H0016044 and H0015099).

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STATEMENT OF CO-AUTHORSHIP

Given that this thesis is presented as a sequence of papers, either published, in press or submitted, statement of co-authorship is provided for each chapter. Due to this thesis format some repetition is expected.

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PUBLICATIONS

All publications listed resulted from work described in this thesis.

Peer-reviewed Journal Publications

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CONFERENCE ABSTRACTS

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4. W Tesfaye, RL Castelino, BC Wimmer, C McKercher, MD Jose, A Neil, ST Zaidi. Medication Burden, Adherence and Health-related Quality of Life in Advanced Chronic Kidney Disease. Australian and New Zealand Society of Nephrology (ANZSN) Annual Congress Darwin, Australia, September 4-6, 2017.
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6. W Tesfaye, RL Castelino, BC Wimmer, C McKercher, MD Jose, GM Peterson, ST Zaidi. Medication Adherence in Adults with Advanced Chronic Kidney Disease. ANZSN Annual Congress in Sydney, Australia, September 10-12, 2018.
7. W Tesfaye, B Wimmer, R Castelino, GM Peterson, M Jose, C McKercher, STR Zaidi. The Effect of Hospitalisation on Potentially Inappropriate Medication Use in Older Adults with Chronic Kidney Disease. European Geriatrics Society Congress in Berlin, Germany, October 10-12, 2018.
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LIST OF ABBREVIATIONS

95% CIs	95% Confidence Intervals
ACR	Albumin Creatinine Ratio
ADL	Activities of Daily Living
AKI	Acute kidney Injury
AUD	Australian Dollars
CCI	Charlson's Comorbidity Index
CG	Cockcroft Gault
CLcr	Creatinine Clearance
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CONT.	Continuous
DMR	Digital Medial Record
eGFR	Estimated Glomerular Filtration Rate
ESKD	End-stage Kidney Disease
GFR	Glomerular Filtration Rate
HbA1c	Glycated Haemoglobin
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Diseases, 10th edition
IQR	Interquartile Range
KDIGO	Kidney Disease Improving Global Outcomes
KDQOL-SF	Kidney Disease and Quality of Life Short Form
KHA-CARI	Kidney Health Australia-Caring for Australasians with Renal Impairment

MAI	Medication Appropriateness Index
MCS	Mental Component Summary
MDRD	Modification of Diet in Renal Disease
MGLS	Morisky Green Levine Scale
MOCA	Montreal Cognitive Assessment
MRCI	Medication Regimen Complexity Index
MRPs	Medication-related Problems
OR	Odds Ratio
PBM	Perceived Burden of Medications
PBS	Pharmaceutical Benefits Scheme
PCS	Physical Component Summary
PIM	Potentially Inappropriate Medication
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RAS	Renin Angiotensin System
RPBS	Repatriation Pharmaceutical Benefits Scheme
RRT	Renal Replacement Therapy
SD	Standard Deviation
SHPA	Society of Hospital Pharmacists of Australia
SPSS	Statistical Package for the Social Sciences
START	Screening Tool to Alert to Right Treatment
STOPP	Screening Tool of Older People's Prescriptions
TABS	Tool for Adherence behaviour Screening
US	United States
USD	United States Dollars
WHO	World Health Organisations

ABSTRACT

The continuous growth in the incidence and prevalence of chronic (non-communicable) diseases, mainly fuelled by an ageing population, has led to an increasing use of multiple medications. In line with this, studies examining medication appropriateness and regimen complexity have been at the forefront of research in recent years, especially in high-risk patients, such as the elderly and those with chronic kidney disease (CKD). CKD is a growing public health problem that affects around 8-16% of the adult population worldwide. It is characterised by a substantial burden of multimorbidity and disease complications leading to the use of multiple medications. This, in turn, poses potential concerns regarding medication appropriateness, regimen feasibility, and adherence. However, despite the high medication burden in patients with CKD, previous studies have mainly focussed on evaluating the dosage appropriateness of renally-cleared and/or nephrotoxic medications. Further, little is published on clinical outcomes associated with medication-related factors in these patients. Therefore, investigating medication-related problems and understanding their determinants in patients with CKD is important in building an evidence base to inform future interventions and practice.

The overarching aim of this thesis was, therefore, to examine medication-related issues and associated outcomes in patients with CKD considering prescriber, regimen, healthcare environment, and patient factors. The specific objectives of the thesis were to: (i) summarise the evidence on the prevalence of inappropriate prescribing, associated clinical outcomes and the potential impact of interventions in CKD; (ii) measure the magnitude of, and evaluate the impact of hospitalisation on, medication inappropriateness in older patients with CKD; (iii) investigate the associations between medication-related factors, including regimen complexity, and risk of hospital readmission in older patients with CKD; (iv) investigate the associations between medication adherence and burden, and health-related quality of life (HRQOL) in adults with advanced pre-dialysis CKD; and (v) evaluate the influence of pharmacist-led medication review on medication appropriateness in older adults with CKD.

To address these objectives, two cohorts including adults with CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73m^2) not receiving renal replacement therapy were examined using retrospective and prospective study designs. The first was a retrospective cohort of older adults (≥ 65 years) with CKD (eGFR 15-60 mL/min/1.73m^2) hospitalised in a tertiary care hospital in Tasmania, Australia over a six-month period (n = 204). The second

cohort included a prospective cohort of adults with advanced pre-dialysis CKD (eGFR < 30 mL/min/1.73m^2) living in the community (n = 101).

A systematic review of the literature was conducted to summarise the magnitude of inappropriate prescribing, associated outcomes and the impact of interventions in patients with CKD. Based on this review of 49 studies, widespread prevalence of potentially inappropriate medications (PIMs) use was observed across a spectrum of the care continuum. The prevalence of PIMs use was 9.4%-81.1% for hospital settings, 13%-80.5% in ambulatory care settings and 16%-38% for long-term care facilities. A small number of studies reported an association between PIMs use and poor clinical outcomes, including prolonged hospitalisation and mortality. Although the heterogeneity between studies precluded a meta-analysis, the number of medications, comorbidities, and age were consistently identified as predictors of PIMs use. This review showed that, despite the regimen complexity in this patient group, previous studies were largely focused on assessing the appropriateness of renally-cleared and/or nephrotoxic medications, rather than more patient-centred outcomes, such as adherence.

Capitalising on the gaps identified in this review, a study was conducted to comprehensively assess medication appropriateness in older patients with CKD recruited via Tasmania's principal tertiary care hospital. The Medication Appropriateness Index (MAI), an implicit set of criteria, was used to assess medication appropriateness, with higher scores on this index corresponding with higher medication inappropriateness. The 2015 Beers criteria, a list of medications recommended to be avoided in older adults or under certain conditions, was also applied to identify PIMs use. Overall, 204 older patients with CKD with a median age of 83 years (IQR 76-87 years) were included. This study revealed that most patients had some level of medication inappropriateness based on MAI (89%), while more than half of them (55%) were taking at least one medication from Beers criteria at hospital admission. A higher number of medications (β 0.72; 95% CI 0.56 to 0.88) and lower eGFR (β 0.11; 95% CI -0.18 to -0.04) were significantly associated with a higher level of medication inappropriateness. Hospitalisation was associated with a small but significant improvement in medication appropriateness in these patients, as shown by a decrease of MAI from admission to discharge (median [IQR]: 6 [3–12] to 5 [2–9]; p<0.01]). The number of patients with at least one PIM from Beers criteria also declined from 55% to 48% during hospitalisation. These findings indicate that, despite an improvement in medication appropriateness during hospitalisation, there was considerable scope for further improvement in medication use for these patients.

In the subsequent two studies, the association between medication-related factors (including medication appropriateness, regimen complexity and the use of selected medications) at hospital discharge and hospital readmission was explored. Overall, people who were readmitted within 30 and 90 days of discharge had a higher level of medication inappropriateness (MAI) compared with their non-readmitted counterparts. Those with higher MAI scores were also likely to be readmitted to hospital relatively sooner within 90 days of discharge. However, after statistical modelling, medication inappropriateness was not independently associated with the occurrence of 30-day (adjusted OR 1.03; 95% CI 0.97-1.09) or 90-day readmissions (adjusted OR 1.06; 95% CI 1.00-1.12). Similarly, regimen complexity (MRCI) was not independently associated with 30-day (adjusted OR 1.27; 95% CI 0.94-1.73) or 90-day readmissions (adjusted OR 1.31; 95% CI 0.99-1.72). However, higher medication regimen complexity (MRCI) was associated with a shorter time to readmission within one year of discharge (HR 1.18 95% CI 1.01-1.36). In contrast, use of renin-angiotensin system blocking drugs was associated with a lower occurrence of 30-day (OR 0.39; 95% CI 0.19-0.79) and 90-day readmissions (OR 0.45; 95% CI 0.24-0.84), and longer time to 90-day readmission (HR 0.52; 95% CI 0.33-0.83).

In the fourth study, the relationships between medication adherence and burden, and HRQOL was assessed using 101 adults with advanced pre-dialysis CKD (eGFR <30mL/min/1.73m^2). The findings of this study showed that medication non-adherence was reported by 43% and 60% of participants using two different self-report adherence measures (Morisky-Green-Levine Scale and the Tool for Adherence Behaviour Screening). Perceived medication burden, but not actual burden, was the main driver of medication non-adherence (adjusted OR 4.89; 95% CI 1.02-23.5). Further, poorer kidney disease-related and generic HRQOL measures were associated with higher regimen complexity (MRCI) and medication non-adherence was associated with a decline in physical HRQOL over time.

In the final study, the effect of hospital pharmacist-led medication review on medication appropriateness was retrospectively assessed in older adults with CKD. Medication appropriateness was evaluated before and after medication review and after acceptance/non-acceptance by physicians of pharmacist recommendations. Of 204 eligible patients, medication review was conducted in 95 (46%). Medication review by pharmacists improved medication appropriateness significantly, as shown by a median MAI reduction from 7 [3-12] to 5 [2-10]; p<0.001. More importantly, medication appropriateness showed greater improvement upon implementation of all pharmacists' recommendations by physicians (median MAI decreased

from 7 to 3; $p<0.05$). Of note, medication appropriateness also improved in patients with no medication review by pharmacists, indicating hospitalisation alone improved medication appropriateness in these patients. However, the overall trend was indicative of greater improvement in medication appropriateness with pharmacist-led medication review, particularly when the recommendations were acted upon by physicians.

In conclusion, this thesis presents a series of interconnected studies that thoroughly examined medication-related factors and their consequences in adults living with CKD. Generally, the studies revealed that these patients are prone to high levels of medication regimen complexity and inappropriateness. People who were readmitted within 30 and 90 days had higher levels of medication inappropriateness and regimen complexity, albeit these variables did not independently predict readmissions within these periods. Further, patients with more complex regimens were more likely to be readmitted relatively sooner within 12 months of discharge. The findings, overall, suggest that these medication-related variables may be important proxy measures of overall health status in this patient group. Also, these findings imply that medication inappropriateness and regimen complexity can be used to prioritise patients who can benefit from optimisation of medication regimens. This is potentially important in contexts like community pharmacies, where there is limited clinical information available for decision-making. The association between renin-angiotensin system blockers use and lowered readmission risk indicates the importance of assessing for ongoing need or potential underprescribing of important medications.

The thesis also identified medication burden, both perceived and actual, to be associated with patient-centred outcomes, including medication non-adherence and health-related quality of life. This finding highlights the importance of assessing and incorporating patient-reported medication experiences and perceptions, along with routine medication review, with the goal of improving medication adherence. Healthcare professionals should actively engage patients in conversations concerning their medications to identify difficulties associated with medication management and adherence. Reiterating the importance of medication adherence in improving the quality of life and slowing disease progression is also instrumental to promote optimal medication use.

Another important finding was the effect of pharmacists' involvement in CKD care. The greater improvement in medication appropriateness after implementation of hospital pharmacists' recommendations by physicians confirms the feasibility and utility of a

multidisciplinary approach in CKD care. However, despite pharmacists' valuable input in optimising medication in these patients, medication review was completed in less than half of included patients. This indicates a need to upscale the role of pharmacists by implementing a standard clinical pharmacy service in all hospitalised patients with CKD. Improved detection of medication-medication and medication-disease interactions and medication non-adherence by pharmacists can be particularly useful to ensure quality use of medicines in this highly vulnerable patient group. Further research is needed to confirm if this is translated into improved clinical outcomes.

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1. CHAPTER ONE: Introduction

1.1. Background

The burden of chronic non-communicable diseases has shown an alarming increase in recent decades mainly due to an ageing population across the globe.[1] Chronic diseases are not only becoming increasingly prevalent but they are now the leading causes of morbidity and mortality, contributing to nearly 70% of all deaths worldwide.[2] The economic consequences of chronic diseases are also enormous due to the combined costs of healthcare and loss of productivity because of illness and premature deaths.[3] Conditions, such as cardiovascular diseases, chronic kidney disease (CKD), cancer and diabetes, are among the leading noncommunicable diseases that put significant burden on global health.[4] The estimated global cost associated with managing cardiovascular diseases, according to a report by World Economic Forum, was USD 863 billion in 2010 and it is projected to rise to USD 1,044 billion in 2030, an increase of 22% after accounting for changing age demographics.[5]

Medicines are the most common form of interventions used for the prevention and treatment of noncommunicable chronic diseases.[3,6] Over the last several decades, the use of multiple medications has shown a significant increase.[4,6] This has been mainly fuelled by the growing need to use multiple medications to treat medical conditions, such as cardiovascular diseases and diabetes mellitus, and to prevent future diseases by managing risk factors.[4,6] The ageing population in different parts of the world is also associated with multiple comorbidities, that require the concomitant use of several medications.[4] Despite the importance of using medications to prevent or delay disease onset, control of diseases and relief of pain, the continual increase in the number of medicines also poses challenges for the patient, healthcare professionals and the healthcare system at large.[7,8]

The use of multiple medications increases the likelihood of adverse drug events, medication-medication and medication-disease interactions, poor medication adherence and preventable medication-related hospitalisations.[9,10] When left unoptimised, medications have also been associated with medication-related morbidity and mortality that is worth more than half a trillion American dollars per annum.[8] Therefore, optimisation of medication therapy, in the milieu of multimorbidity and polypharmacy, is a challenge with an impact on health outcomes and healthcare expenditure.[8] As such, researchers in recent years have put greater emphasis on evaluating medication appropriateness and its health consequences, particularly focusing on the older population.

Patients with CKD are among patient groups with one of the highest medication burdens.[11] This is because of the various treatment goals aimed at preserving renal function (or slowing disease progression), treating multiple comorbidities, and managing disease-related complications.[11] The high number of comorbidities and associated use of multiple medications in patients with CKD, in turn, predisposes patients to different medication-related harms.[12] The primary concern in patients with CKD is that many medications rely on the renal route for clearance from the body.[13] Therefore, upon renal impairment, patients will have a reduced ability to eliminate these medications, leading to plasma accumulation and possibly associated toxicity.[14,15]

The altered pharmacokinetic and pharmacodynamic profiles in patients with CKD make dose adjustment and/or avoidance of most renally-cleared medications necessary.[15] Accordingly, studies have widely examined inappropriate prescribing of renally-cleared medications across a spectrum of patients with CKD in different health settings.[16,17] However, the quality use of medicines in patients with CKD is multi-faceted; it encompasses underuse of recommended preventive therapies, as well as dosage adjustments and avoiding potentially inappropriate medications (PIMs) use.[13] Therefore, evaluation of medication appropriateness that transcends the mere checking of dosage appropriateness of renally-cleared medications can be useful in identifying areas of improvement.

The second concern in CKD management relates to the complex regimens used by most patients. In addition to the number of medications, other medication characteristics like the dosage form, dosing frequency and additional medication instructions involved can also contribute to regimen complexity.[18] Evidence suggests that medication regimen complexity, quantified considering these variables, may have an impact on health outcomes in older adults.[19,20] Therefore, understanding the association between medication regimen complexity and different health outcomes in patients with CKD is important to identify patients who can benefit from regimen simplification strategies.

In addition to medication appropriateness and regimen complexity, another important consideration in chronic disease prevention and management is medication adherence.[21] Medication adherence is defined by the World Health Organization (WHO) as 'the extent to which an individual complies with agreed recommendations from healthcare providers about their medications.'[11] However, despite the importance of medication adherence in improving health outcomes, the prevalence of non-adherence among patients receiving medications for

chronic diseases ranges between 43% and 78%.[22] Similarly, suboptimal medication adherence is commonly reported in patients with CKD, although previous studies were highly focussed on people with end-stage kidney disease (ESKD).[23]

Factors affecting medication adherence are broadly categorised into five domains: patient, therapy, socioeconomic, healthcare system, and condition factors.[24] These factors are also relevant in predicting medication adherence in patients with CKD.[23] Studies showed that therapy-related factors, such as regimen complexity and perceived medication burden, have been linked with adherence in patients with CKD, albeit inconsistently.[23,25] Identifying therapy-related factors affecting adherence in patients with CKD is important to propose a multifaceted intervention that integrates these factors with other patient and system-based factors to improve adherence. Understanding the interplay among medication burden, adherence and patient-centred outcomes in patients with CKD is also in line with a call for a concerted effort to establish optimal patient-centred care.[24]

1.2. Literature review

1.2.1. Medication utilisation patterns and trends

In Australia, medication use has increased enormously in recent decades.[6,26] The National Health Survey of 1995 revealed that 10.7 million people reported having used one or more medications, comprising more than half of the population at the time (59%).[27] Another study conducted 15 years later between 2009-2010, surveying 4,500 Australians aged 50 years and above showed a much higher proportion of medication use, as reported by 87% of the participants.[6] The combined Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS) prescription counts have also shown a 63% increase from 133,568,781 prescriptions in 1997 to 217,220,377 in 2015.[26] This is to be compared with a population growth of nearly 28% over the same period. The rise in the use of medications is mainly driven by the increasingly ageing population, the growing prevalence in chronic diseases, and decreasing mortality rates.[28,29] For instance, the National Health Survey of Australia reported an increase in the proportion of people with at least one chronic condition from 42.2% to 47.3% between 2007-08 and 2017-18.[29]

Cardiovascular agents constitute the major class of medications that has shown a remarkable growth in volume in recent decades in Australia (Figure 1.1.).[28] In particular, as shown in the Figure 1.1., a steep increase in medication use was observed between the late 1990s and early 2000s. Medications acting on the nervous system and anti-infectives for systemic use were among other classes of medications that also showed a substantial increase during the same period.[28]

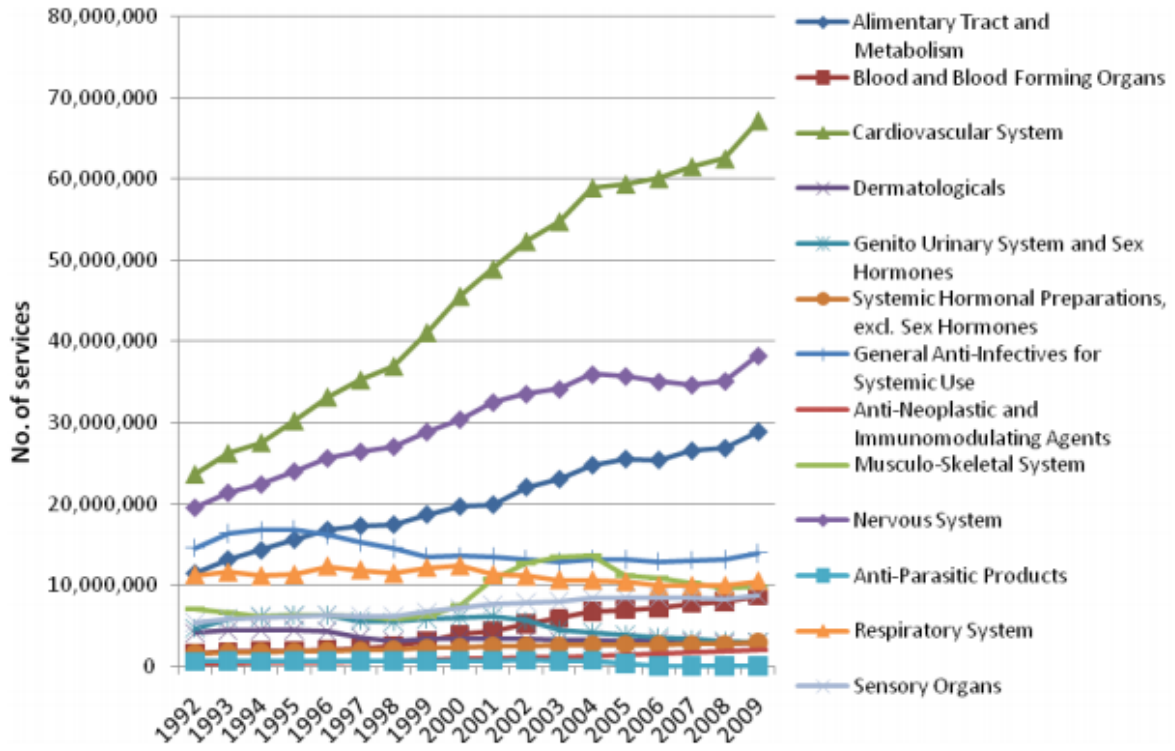


Figure 1.1. Medication volume (services) for various medications dispensed in Australia between 1992-2009 (total of PBS and RPBS)[28]

The use of prescription medicines has also shown an increasing trend for over half a century in the Unites States (US).[4] Between 1988-1994 to 2007-2010, while the number of people (of all ages) who did not take any regular medication(s) has decreased from almost 61% to 52.5%, the percentage of those on polypharmacy (defined as taking five or more prescription medications) increased from 4% to 10% (Figure 1.2.). This equates to half of all Americans with at least one prescription medication.[4] Further, another study in the US also reported an increase in the use of prescription medications from 51% to 59% of adults between 1999-2000 and 2011-2012, with a corresponding increase in the prevalence of polypharmacy from 8.2% to 15% for the same period.[30]

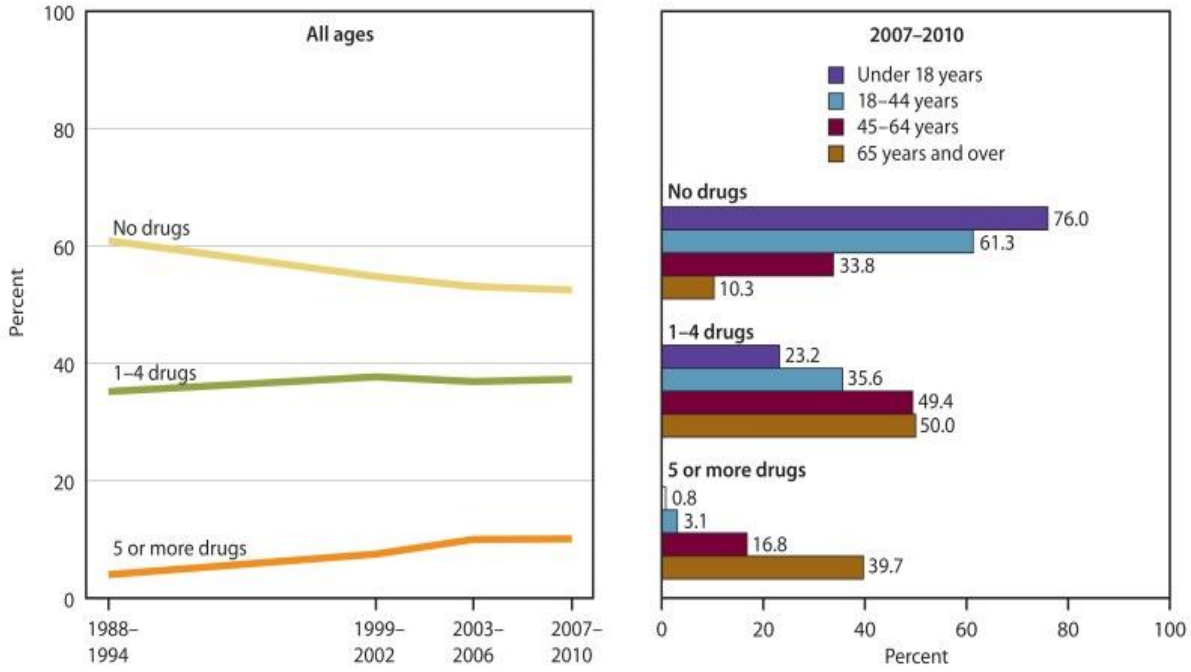


Figure 1.2. The use of prescription medications, by the number of drugs taken and age: United States, 1988-1994 to 2007-2010[4]

The increase in the use of prescription medications is mainly driven by an ageing population across the globe, the rise in incidence and prevalence of chronic diseases and the development of various disease-specific clinical practice guidelines.[3,4,31] Medication research targeted at better treatment and management of risk factors for chronic conditions, including hypertension, congestive heart failure, high cholesterol and diabetes also led to increased medication use.[4] However, this increase could also be attributed to other factors, such as the development of newer medications for the treatment of communicable and non-communicable diseases, the widespread availability of medications and the growth of marketing strategies by the pharmaceutical companies.[4,32] Compared to communicable diseases, chronic non-communicable diseases have been associated with a significant increase in the use of multiple medications.[4] Diseases, such as cancer, cardiovascular conditions (e.g. hypertension, heart failure and dyslipidaemia), kidney diseases, diabetes and depression are among those in which medication use has shown an increasing pattern. (Figure 1.3.)

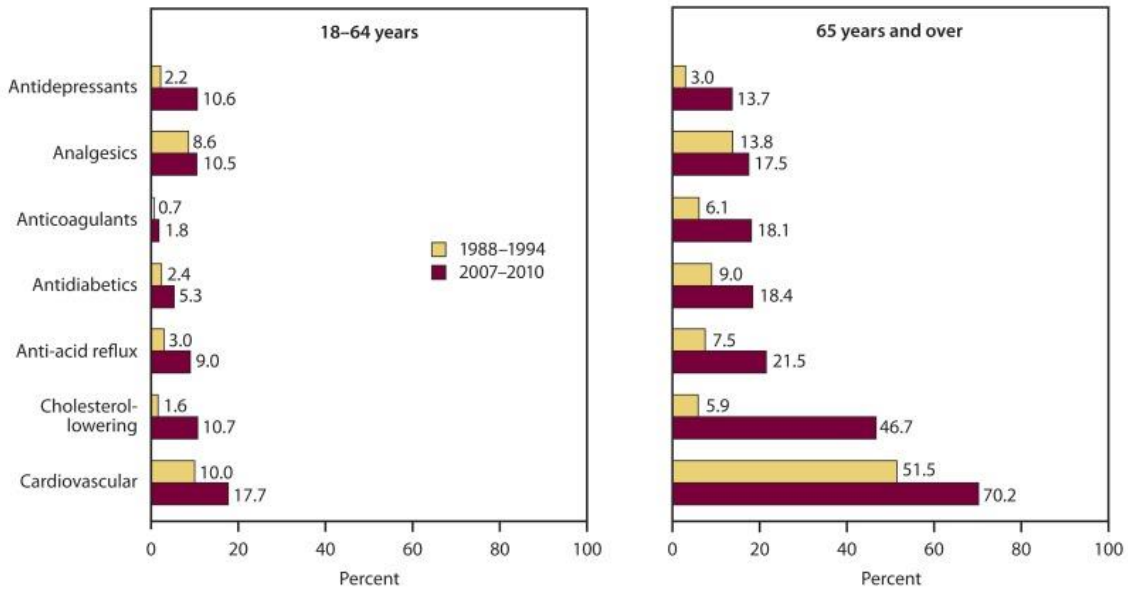


Figure 1.3. Prescription medication use in the past 30 days among adults aged 18 and over, by age and selected drug class: United States, 1988–1994 and 2007–2010[4]

1.2.2. Medication appropriateness

1.2.2.1. Definition of medication appropriateness

The use of multiple prescription medications, although quintessential in the management of chronic diseases, can potentially lead to detrimental outcomes, especially if left unoptimised.[8] Medication-related problems (MRPs) is an umbrella term used to describe problems that occur due to the use of medications. The concept of MRP originates after the idea of pharmaceutical care came to the fore at the beginning of the 1990s.[33] Pharmaceutical care, according to Helper and Strand, '…is a quality improvement process in which the professional improves the outcomes of pharmacotherapy.'[34] This quality improvement process encompasses the identification of the causes that potentially lead to the problem and addressing it.[33] The philosophy of pharmaceutical care, in turn, leads to the concept of MRPs.[33] As such, MRP was first defined by Strand et al as 'an undesirable patient experience that involves medication therapy and that actually or potentially interferes with patient outcome.'[35] This definition contains eight conceptual categories that healthcare professionals can use to identify or characterise MRPs. These include the presence of an indication that requires a medication, appropriateness of the medication for the given indication, under- and over-dosing of medications, presence of a medical condition resulting from an adverse drug reaction of medications, presence of drug-drug, drug-food and drug-laboratory interactions, presence of a medical condition not receiving the recommended prescribed medication, and having a

medication with no valid indication.[35] These MRPs are important not only in terms of standardising the clinical care that patients receive, but also because they are potentially modifiable through detection, treatment and, most importantly, prevention by healthcare practitioners.

The Pharmaceutical Care Network Europe also defined MRPs almost similarly as: 'event(s) or circumstance(s) involving drug therapy that actually or potentially interferes with desired health outcomes.'[33] This classification has a broad category of domains consisting of problems, causes and interventions. A problem is defined as 'the expected or unexpected event or circumstance that is, or might be wrong, in therapy with medicines.' The 'cause' part assesses the action, or lack thereof, that leads to the occurrence of potential problems. This could relate to medication selection, the patient's proper use of medication, lack or misinterpretation of information, personality of the patient or logistics of prescribing/dispensing. The 'intervention' section looks at the different measures taken to correct the causes of MRPs. Each of these categories has sub-domains that enable evaluators to capture problems at patient, medication and prescriber levels.[33]

Although several other criteria and definitions of MRPs have emerged from different research groups, none of these tools could be easily implemented in clinical practice.[36] However, in an effort to easily integrate prescribing quality assessment in routine practice, especially in the older population, several criteria have been developed. These criteria are broadly classified into implicit and explicit measures. The implicit criteria are patient-specific approaches that require access to an array of medical and laboratory information to assess the appropriateness of individual medications.[37] The focus of explicit criteria is to identify PIMs whose risk outweigh the benefit and, therefore, are best to be avoided in older adults or under certain disease conditions.[37] Although the development of these criteria simplified the evaluation of medication inappropriateness in older adults, the time they take and the lack of a gold-standard measure of medication appropriateness have made their integration into clinical practice challenging.

The Medication Appropriateness Index (MAI),[38] commonly used implicit criteria, was initially developed in 1992 to measure the quality of care in healthcare services and to assess changes in prescribing over time.[38] Subsequent research has shown that this tool has an acceptable intra- and inter-rater reliability, and predictive validity in older populations in different health contexts.[39] This tool consists of 10 pharmacotherapeutic components: indication, effectiveness,

dosage, directions for use and practicality of the directions, drug-drug and drug-disease interactions, the relative expense of medications, duplication of therapy and duration of treatment. Each criterion has rating instructions to assess its appropriateness. For items rated as inappropriate, weighted scores ranging between 1 and 3 (e.g. 3 for "indication", 2 for "drug interactions" and 1 for "therapeutic duplication") are used to calculate the MAI score for medications. The MAI scores per patient are then obtained based on the summation of the MAI scores of individual medications. The MAI scores for each medication range between 0 and 18, with higher MAI scores corresponding with a higher level of medication inappropriateness. However, the need for detailed clinical data and the time it takes to assess individual medications limits the applicability of implicit tools such as the MAI in practical settings. Therefore, researchers have developed explicit and easy-to-use approaches to capture prescribing quality in the older population, which require less time and medication information.

Several explicit measures have been developed to identify PIMs use in older adults.[40] Explicit tools comprise a list of medications that are recommended to be avoided in older people or under certain conditions because the risk associated with the use of these medications generally outweighs their benefit. The American Geriatrics Society was a pioneer in developing the first explicit measure of inappropriate medication use in 1991 and, given its relevance and application for research and clinical practice, it has been updated numerous times since.[41-45] Following the development of the first Beers criteria, several explicit measures were developed aiming to improve the identification of PIMs use in the older population.[46-54] Of these tools, the screening tool of older people's prescriptions (STOPP) and screening tool to alert to right treatment (START) criteria were the most notable and widely accepted in research.[47] This is mainly because, in addition to medications to be avoided, the STOPP-START criteria also consider potential prescription omissions in medication assessment. The Beers criteria were also updated in 2015 and 2019 considering newer evidence emerging from the latest literature.[45,54] However, the explicit criteria available are somewhat limited because of their lack of depth in terms of assessing medication appropriateness using detailed laboratory and clinical information. This is because these tools often categorically identify medications to be avoided in older adults, rather than considering other relevant individual pharmacotherapeutic aspects, such as dosage appropriateness, concomitant conditions, indication, drug-drug, drug-laboratory and drug-disease interactions and duplication of therapy, among others.

Australian-specific prescribing quality indicators have also been developed for use in older adults.[50,55,56] The original tool that was developed by Basger et al contains 48 prescribing

indicators based on medications and health conditions that are common in Australian settings.[56] This tool mainly consists of explicit indicators (45 out of 48 items) that are used to assess under- and over-treatment in older adults.[55] However, despite the relevance of having a setting-specific tool to identify PIMs use, most of the limitations of explicit criteria mentioned above are more or less applicable to these Australian tools alike.

1.2.2.2. Extent of medication inappropriateness

Medication inappropriateness, and its association with different clinical and patient outcomes, has been targeted by several studies. A systematic review by Morin *et al* reported that the prevalence of PIMs use has significantly increased from 30.3% in studies conducted between 1990-1999 to 49.8% in those conducted after the year 2005 ($p<0.01$).[57] Another study corroborates this evidence showing that the odds of exposure to PIMs showed an average 11% per year increase between 2005 and 2015.[58] Furthermore, a significant proportion of people in residential care homes receive PIMs (overall weighted point prevalence: 43%), with the prevalence showing an increasing trend over time.[57,58]

The review by Morin *et al* also indicated that the prescribing of PIMs in European nursing homes was relatively higher than that from the North American and other countries.[57] In comparison, an Australian study that targeted 2,345 aged care residents reported that about 35% of them were receiving at least one PIM as defined by the Beers criteria.[59] A comparable prevalence of 30% was reported in a study specifically targeting older Australians with dementia residing in residential aged care facilities.[60]

Several studies have assessed medication inappropriateness in a hospital setting.[61-63] A study consisting of 195 older adults from the United Kingdom reported a PIMs prevalence of 26.7% upon patients' hospital admission.[61] On the other hand, various ranges of PIMs use were reported in a study performed in six countries across Europe.[64] The prevalence in these countries varied depending on the tool used to assess medication inappropriateness. For example, while the prevalence of PIMs use ranged between 34.7% in Prague to 77.3% in Geneva when the STOPP criteria were applied, the prevalence varied from 22.7% to 43.3% when Beers criteria were applied.[64] Other studies from Australia reported that more than 52% and 55% of the targeted patients were receiving at least one PIM based on the STOPP criteria at hospital admission.[63] A recent study from the US also reported a relatively higher level of PIMs use at hospital admission, which varied depending on the tool applied – 62.3% based on Beers criteria and 43.4% using STOPP criteria.[62]

Based on a systematic review of studies from eleven countries, the prevalence of PIMs use in primary care is generally lower than that in hospital and residential care settings, and widely varies between 2.9 and 38.5%.[65] Similarly, another systematic review targeting community-dwelling older adults in European countries reported an overall weighted prevalence of PIMs use of 22%, which is lower than for people in residential care facilities.[66] On the other hand, studies from the US and Canada reported a prevalence of 29% and 31% in community-dwelling older adults, respectively.[67]

1.2.2.3. Outcomes associated with medication inappropriateness

Medication inappropriateness is not only an indicator of poor prescribing practice, but it has the potential to lead to detrimental clinical and patient outcomes. However, despite the increasing number of publications focusing on the evaluation of medication (in)appropriateness in the older population using different criteria, limited data is available on clinical outcomes attributed to PIMs use. Of these, a study conducted in Australia revealed that exposure to PIMs from Beers criteria was associated with frequent unplanned hospitalisations in older adults.[68,69] Further, people prescribed with multiple PIMs (≥ two) were more likely to experience other negative outcomes, including longer hospitalisations and higher hospital costs than those with one PIM.[70] Similarly, in older community-dwelling patients, the use of two or more PIMs (defined based on the STOPP criteria) was associated with poorer HRQOL and increased emergency visits over a two-year period.[71] Another study targeting people discharged from hospital indicated that inappropriate prescribing, as defined based on Beers criteria, was associated with poor medication adherence after hospital discharge.[72] A review of the economic impact of PIMs use in older adults showed that the use of PIMs was associated with higher health care utilisation and increased healthcare expenditure compared with no use of PIMs.[73] Moreover, the estimated annual cost of morbidity and mortality due to nonoptimised medication therapy in the US is reported to exceed half a trillion dollars.[8]

1.2.2.4. Determinants of medication inappropriateness

In addition to reporting the prevalence of medication inappropriateness, several studies have identified factors associated with the use of PIMs. A higher number of medications, living in residential care homes, advanced age, female gender, presence of depression, low functional status and low socioeconomic status were among the factors associated with PIMs use.[57,66] Particularly, medication-related factors, such as the number of medications and regimen

complexity, are modifiable factors that are consistently and independently associated with the use of PIMs in older people.[57,66]

1.2.2.5. The role of interventions in optimising medications

The high prevalence of PIMs reported by different studies, along with associated clinical consequences, have prompted the implementation of different interventions. These include manual interventions (mostly involving pharmacist-led medication reviews) and integration of computerised decision support systems into the usual clinical care.[74] The paradigm shift in pharmacy practice in recent decades, from the old product-oriented to a more patient-oriented program, has provided pharmacists with the opportunity to improve inpatient care.[75] The unique training pharmacists now receive about pharmacotherapy has equipped them with the necessary training to be involved in therapeutic decision-making.[75] The involvement of pharmacists in the primary care setting has also led to improved and cost-effective services.[76]

Owing to these developments, the scope of pharmacy training in different parts of the world is expanding in ways that foster collaborations between pharmacists and physicians across the care continuum.[77,78] This ranges from involving pharmacists in collaborative medication management in the US to the implementation of independent pharmacist prescribing models in the United Kingdom.[77-79] The staggering economic burden associated with nonoptimised medications also increases the pivotal role pharmacists will have in the foreseeable future.[8]

Medication reconciliation is one of the well-established roles of clinical pharmacists that is implemented in different health settings. This involves querying patients about the medications they take to obtain an accurate and updated list of medications and has become part of clinical care in most hospitals and across the care continuum since its introduction. Improved detection of medication discrepancies is observed with pharmacist-led medication reconciliation when compared with usual care.[80] Further, medication reconciliation by pharmacists is associated with improved healthcare utilisation after hospital discharge.[81]

Another important role of pharmacists as part of clinical pharmacy services is medication review and therapy management to ensure the appropriateness and safety of medications. In line with this, the impact of pharmacist-led medication review in optimising older peoples' medications has been explored across different settings.[82,83] Studies reported that involving pharmacists in a multidisciplinary team in primary and secondary geriatric care can improve medication appropriateness in older people.[82,83] These interventions involving pharmacists are

more beneficial to patients with complex disease status and medication regimens, including patients with CKD.[84] However, a recent review by Rankin *et al* showed that while pharmaceutical care was relevant in slightly reducing prescription omissions, it had little effect in reducing negative outcomes, such as hospital admissions and quality of life.[74]

Rankin et al assessed the impact of pharmaceutical care in the form of medication reviews by different healthcare professionals, including general physicians, pharmacists and geriatricians.[74] The results revealed that pharmaceutical care did not result in a significant improvement in medication appropriateness, measured via both implicit and explicit criteria.[74] The review showed that interventions that involved multidisciplinary and clinical decision support system components were relatively effective.[74] However, the review is generally limited for including studies that were of relatively poor quality.

1.2.3. Chronic kidney disease (CKD) and its management

1.2.3.1. Definition and classification of CKD

The Kidney Disease Improving Global Outcomes (KDIGO) and Kidney Health Australia's Caring for Australasians with Renal Impairment (KHA-CARI) define CKD based on abnormalities of kidney structure or function lasting for at least three months, with implications for health.[85,86] The diagnosis of CKD relies on the presence of at least one of the following criteria for at least three months: a decreased glomerular filtration rate (GFR) of < 60 mL/min/1.73m^2 and/or having indicators of kidney damage (based on albumin-creatinine ratio (ACR) ≥ 30 mg/g and albumin excretion ratio of ≥ 30 mg/24h).[86,87] The GFR cut-off value of 60 mL/min/1.73m^2 is used to define CKD because this value is considered to be less than half of the normal renal filtration rate in young adult men and women (~125 mL/min/1.73m^2). An ACR of 30 mg/g is also three times greater than the normal value in healthy adults and is thus used as a reference value.[85]

CKD is traditionally classified into five stages based on GFR (often estimated GFR; eGFR). In this classification, people with eGFR < 90 mL/min/1.73m^2 are considered to have some form of renal impairment.[85] However, due to the association of lower eGFR and higher albuminuria values with increased cardiovascular events, acute kidney injury, disease progression, and mortality, both of these criteria have become an integral part of CKD staging.[85,88] As such, the classification of CKD based on disease cause, eGFR and albuminuria categories provides a more accurate classification and has greater prognostic value.[88] Based on these considerations

the staging of CKD is modified into six eGFR (G) and three albuminuria (A) categories, as shown in Figure 1.4. below.[85]

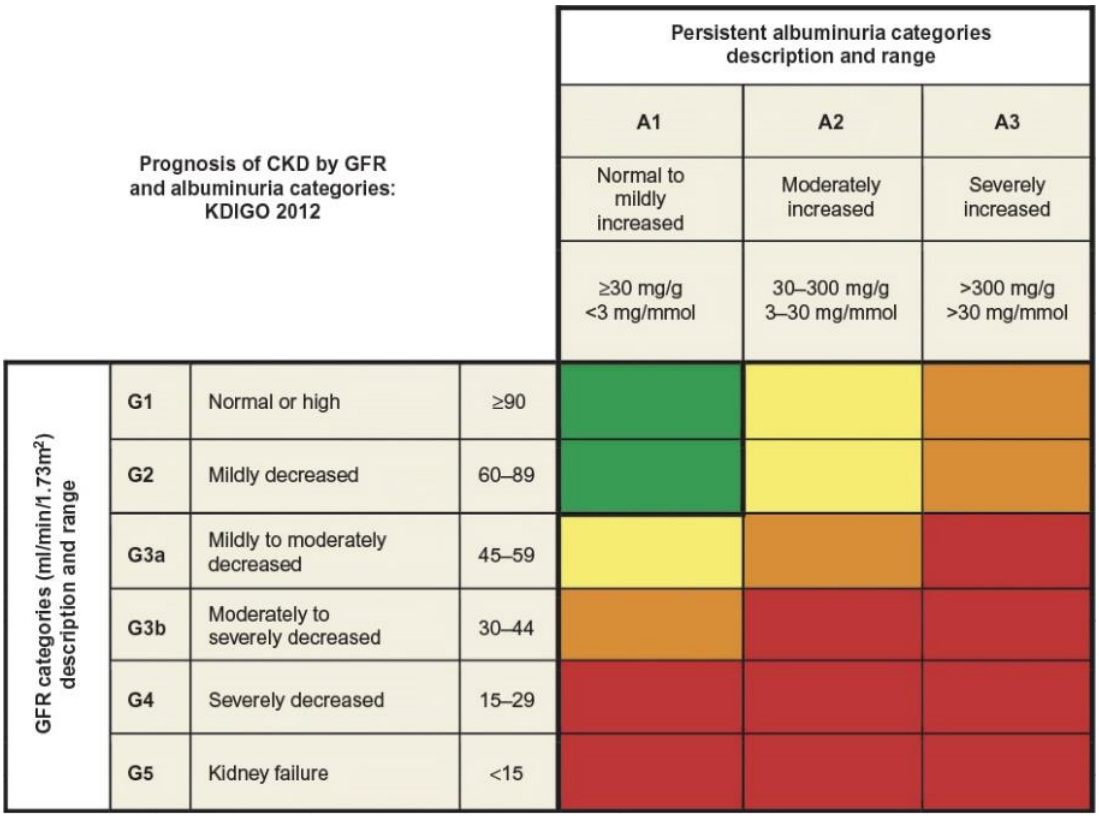


Figure 1.4. Staging of chronic kidney disease (CKD) based on glomerular filtration rate and albuminuria[85]

1.2.3.2. Epidemiology of CKD

CKD is a growing public health problem that affects 8-16% of the adult population worldwide.[89] The global mean prevalence of CKD is estimated at 13.4%, with stage three CKD (eGFR: 30-59 mL/min/1.73m^2) contributing to the majority (80-90%) of the reported cases.[89,90] High-income countries, including the US, Canada, and Australia, are more affected by CKD than developing nations.[90] The prevalence (in adults) in these countries is reported to be around 11%.[91] Moreover, the epidemiology of CKD also varies depending on ethnicity and social class within these countries.[91] This is shown by a significantly higher CKD prevalence in people in the lowest socioeconomic quartile (compared to the highest), ethnic minorities in the UK (African and Asian people) and the US (Hispanics), and Indigenous people in Australia, New Zealand and Canada.[91] Although the burden of CKD is more pronounced in developed regions of the world, it is expected to become a substantial burden in developing and developed nations alike.[89,90] This is mainly due to the expanding older population in countries like China and

India.[89] The incidence of end-stage kidney disease (ESKD) is similarly rising in different parts of the world.[89] Although most patients (>80%) receiving treatment for ESKD are from highly-developed countries, the incidence of ESKD is also showing a disproportionate increase in developing countries.[92]

1.2.3.3. Causes and risk factors of CKD

The main causes of CKD in developed countries and most developing countries are diabetes and hypertension.[89] Glomerulonephritis is the third most common cause of CKD, especially in Asian and sub-Saharan countries.[89] In Australia, diabetes, glomerulonephritis, and hypertension are the three most common causes of kidney diseases.[93] In addition to the continuously rising burden of non-communicable diseases, the increasing number of people living to old age also leads to an increased prevalence of CKD.[94] (Figure 1.5.)

In contrast, infectious diseases, environmental pollution by heavy metals, pesticides, abuse of analgesics and unregulated food additives are among other causes of CKD in developing settings.[89] Human Immunodeficiency Virus is an infectious cause of CKD in sub-Saharan Africa.[91] The double-burden of infections and chronic noncommunicable diseases is, therefore, believed to bring future challenge in developing settings.[89] Herbal medicines, often common in rural populations of Africa and Asia, can also have nephrotoxic effects leading to CKD, acute kidney injury (AKI) and electrolyte disturbances.[89,91] Low birthweight and poststreptococcal glomerulonephritis are identified as indicators of kidney disease in remote-living Aboriginal people.[95] Genetic causes of CKD involving single or multiple genes have also been identified.[91] These include congenital anomalies since birth or childhood or autosomal dominant polycystic kidney disease, which occurs later in life.[91,96] Polycystic kidney disease currently affects more than half a million people in the US and is responsible for nearly 5% of all ESKD cases.[96]

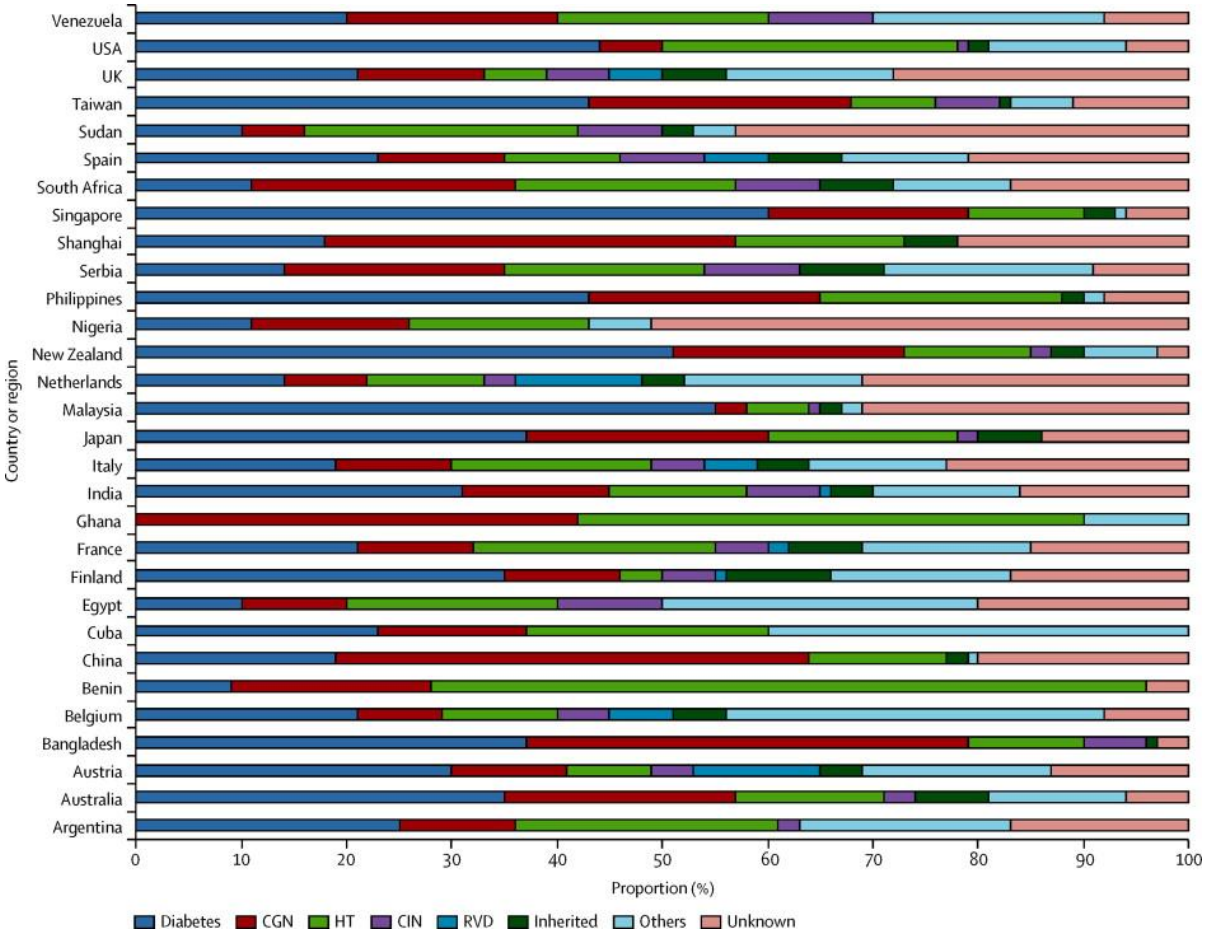


Figure 1.5. The worldwide distribution of causes of chronic kidney disease[89]

(CGN, chronic glomerulonephritis; HT, hypertensive nephrosclerosis; CIN, chronic interstitial nephritis; RVD, renovascular disease.)

In addition to the causes of CKD mentioned above, various risk factors (both modifiable and non-modifiable) are associated with an increased risk of developing CKD. These factors can be broadly categorised into clinical and sociodemographic risk factors. Diabetes, hypertension, autoimmune diseases, obesity, tobacco smoking, family history of CKD, neoplasm, AKI, infection and low birth weight are among some of the clinical factors that increase the risk of developing CKD.[59,95,97] On the other hand, older age, ethnicity (African American, American Indian, Hispanic, Asian or Pacific Islander) and low socioeconomic status are among the sociodemographic factors that contribute to increased risk of CKD.[89] Gender differences have been observed in CKD epidemiology; while women are generally more affected by CKD (pre-dialysis) than men, the incidence of RRT is higher in men.[98] These disparities could be partly due to longer life expectancy in women, hormonal differences, faster disease progression in men, differences in access to care and preference (women have reduced access to kidney donors and greater tendency to choose conservative care).[98]

1.2.3.4. Medications as causes of CKD

Another important and, in most cases, modifiable cause of kidney diseases is exposure to nephrotoxic medications.[99] Prolonged exposure to non-steroidal anti-inflammatory medications is among the most common medication causes of CKD.[99] Other medications, including aminoglycosides antibiotics (especially when their doses are unadjusted), lithium and radiographic contrast materials, are among those with nephrotoxic effects.[99] The use of nephrotoxic medications is particularly common in hospitalised patients.[99] Exposure to nephrotoxic medications is associated with increased risk AKI, irreversible loss of renal function and other costly adverse drug events.[100] Figure 1.6. shows a list of medications with nephrotoxic effects. Of note, this figure contains a list of nephrotoxic medications based on an American study[101] and is not an exhaustive list of all nephrotoxic medications.

Acyclovir	Enalaprilat	Mesalamine
Ambisome[a]	Foscarnet	Methotrexate
Amikacin	Gadopentetate dimeglumine[a]	Nafcillin
Amphotericin B	Gadoextate disodium[a]	Piperacillin/tazobactam
Captopril	Ganciclovir	Piperacillin
Carboplatin	Gentamicin	Sirolimus
Cefotaxime	Ibuprofen	Sulfasalazine
Ceftazidime	Ifosfamide	Tacrolimus
Cefuroxime	Iodixanol [a]	Ticarcillin/clavulanic acid
Cidofovir[a]	Iohexol[a]	Tobramycin
Cisplatin	Iopamidol[a]	Topiramate
Colistimethate	Ioversol[a]	Valacyclovir
Cyclosporine	Ketorolac	Valganciclovir
Dapsone	Lisinopril	Vancomycin
Enalapril	Lithium	Zonisamide

[a]Medications counted for 7 days after administration toward exposure due to their long half-life. All other listed medications count for 48 additional hours after exposure.

Figure 1.6. List of nephrotoxic medications[101]

1.2.3.5. Consequences of CKD

CKD is associated with a substantial increased risk of morbidity and mortality. According to the Global Burden of Disease study, the absolute number of deaths due to CKD rose by 34% (from 920, 000 to 1, 230, 000) from 2007 to 2017.[1] However, the age-standardised annual

death rates remained relatively stable, showing an increase of 1.5%.[1] Further, the same dataset shows a rise in disability-adjusted life years of 52.6% in patients with CKD (from 1, 269, 049 to 1, 935, 954) and an increase in death due to CKD of 58.3% (from 52, 127 to 82, 539) between 2002 and 2016.[102] Patients with CKD also have comparably higher rates of hospitalisation and hospital readmission compared with people with no CKD.[103] In the US, the rate of hospitalisation in CKD in 2012 was 1.73 per patient year, with 35.2% of people on dialysis readmitted to hospital within 30 days of discharge.[103]

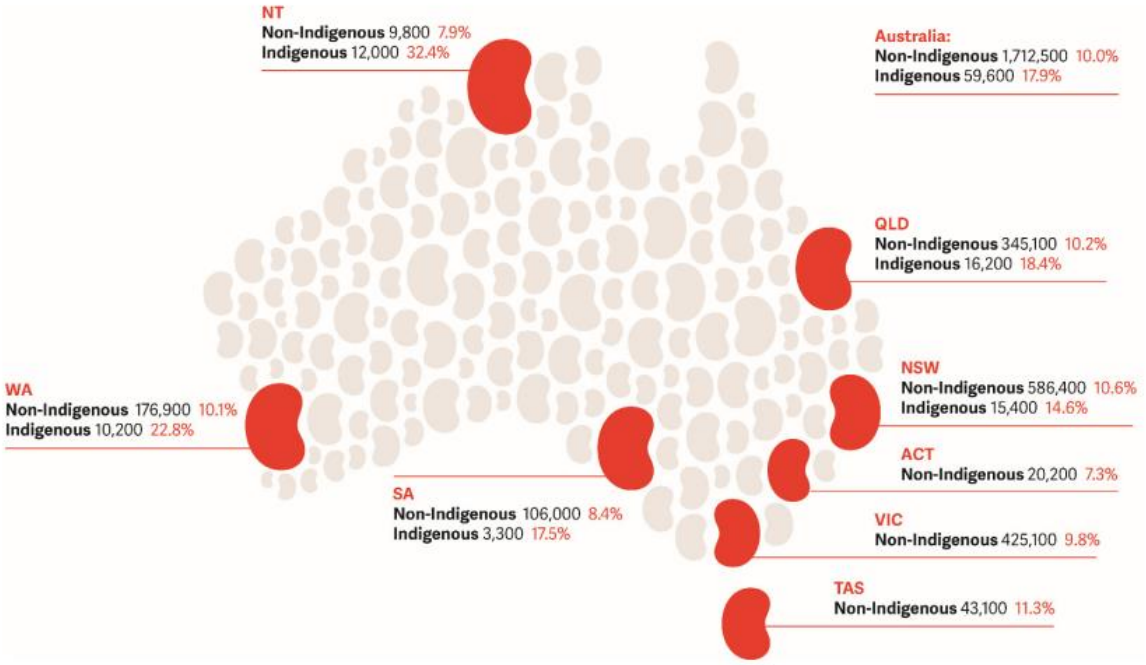
CKD imposes a tremendous economic burden on healthcare expenditure. High-income countries spend a disproportionate 2-3% of their annual healthcare budget for the treatment of ESKD, despite this patient group representing only less than 0.3% of their total population.[89] The cost of treating pre-ESKD patients is even higher than that for ESKD treatment. For example, in 2015, the US government spent USD 64 billion for the treatment of general CKD compared with USD 34 billion for ESKD treatment.[104] Similarly, in the United Kingdom, the National Health Service estimated that CKD was responsible for the 1.3% of total healthcare spending in the year 2009-10.[89] Additionally, CKD contributes to the increased healthcare spending in diabetes and hypertension patients.[104]

1.2.3.6. CKD in the Australian context: epidemiology and consequences

The burden of CKD has been growing in the Australian context over the last decades and has now become the 10th leading cause of death.[93,105] It was estimated that around 1.7 million Australian adults (1 in 10) have some biomedical signs of CKD, whereas 1 in 3 is at increased risk of eventually developing it.[106] The prevalence is even higher in older adults (with the risk nearly quadrupled in those aged 75 years or older), men, and in those with low socioeconomic status.[107] Further, Indigenous Australians have double the risk of their non-Indigenous counterparts in terms of showing the biomedical signs of CKD.[17] (Figure 1.7.)

The incidence and prevalence of ESKD patients on renal replacement therapy (RRT) has also markedly increased in Australia since its implementation in the 1960s (Figure 1.8.).[108] There were 3,056 new cases of RRT patients in 2017 (overall incidence rate of 124 per million population), showing a 70% increase from the 1,723 cases reported in 2000 (90 per million population).[108] Similarly, in 2017, a total of 24,738 people (i.e. 1006 per million population) were receiving RRT.[108] The incidence of RRT in Australia was projected to grow by 60% (from 19,780 to 31,589) between 2011 and 2020, and is expected to double in those aged ≥75 years.[109] The incidence has also shown a disparity in trend based on patient and equity status. Males (1.5

times as high compared with females), people living in remote and very remote areas (twice as high compared to major cities) and those with low socio-economic status (1.6 times as high in



the lowest compared with the highest socioeconomic group) being at a higher risk of developing ESKD.[109]

Figure 1.7. The number (proportion) of people living with biomedical signs of CKD in Australia, by indigenous status and geographical location (2013)[110]

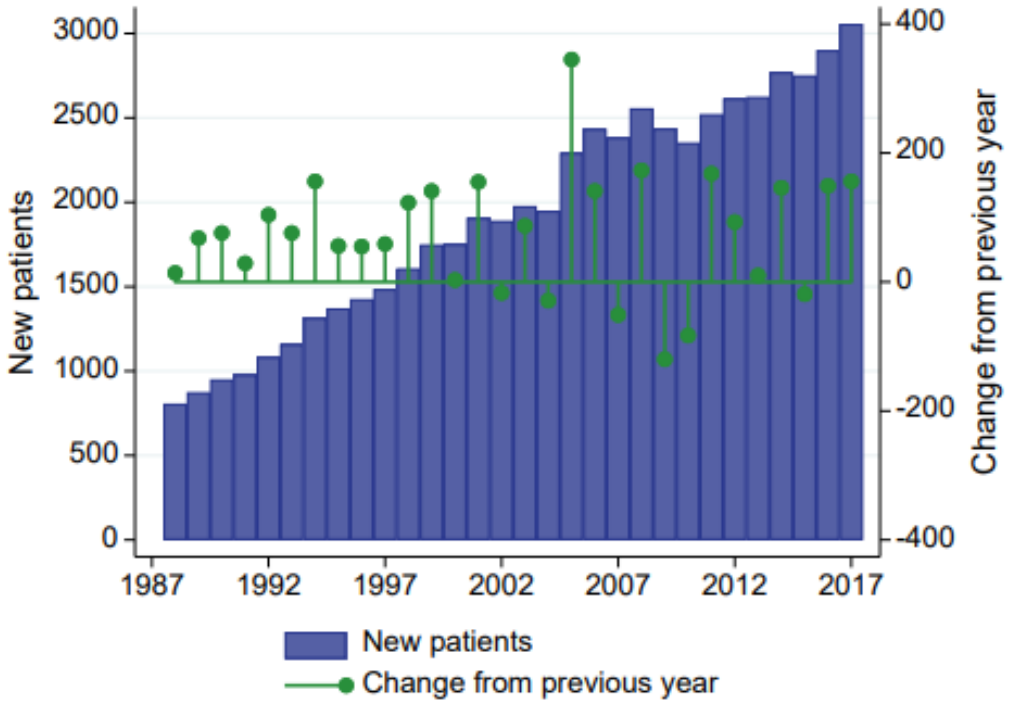


Figure 1.8. The number of new patients on renal replacement therapy and the change over the last 30 years[108]

CKD is a cause of significant morbidity and mortality in Australia, especially in older adults. For example, a total of 43,600 hospitalisations (excluding regular dialysis episodes) had CKD as the principal diagnosis from 2015-2016.[11] This represented 16% of overall hospitalisations in Australia during this time and an increase of 51% since the year 2005-2006.[107] The age-standardised hospitalisation rate, over the same period, had also increased by 22% from 138 to 169 per 100,000 population.[107] (Figure 1.9.) Hospitalisation due to CKD is five times higher in Indigenous Australians than for non-Indigenous Australians.[107]

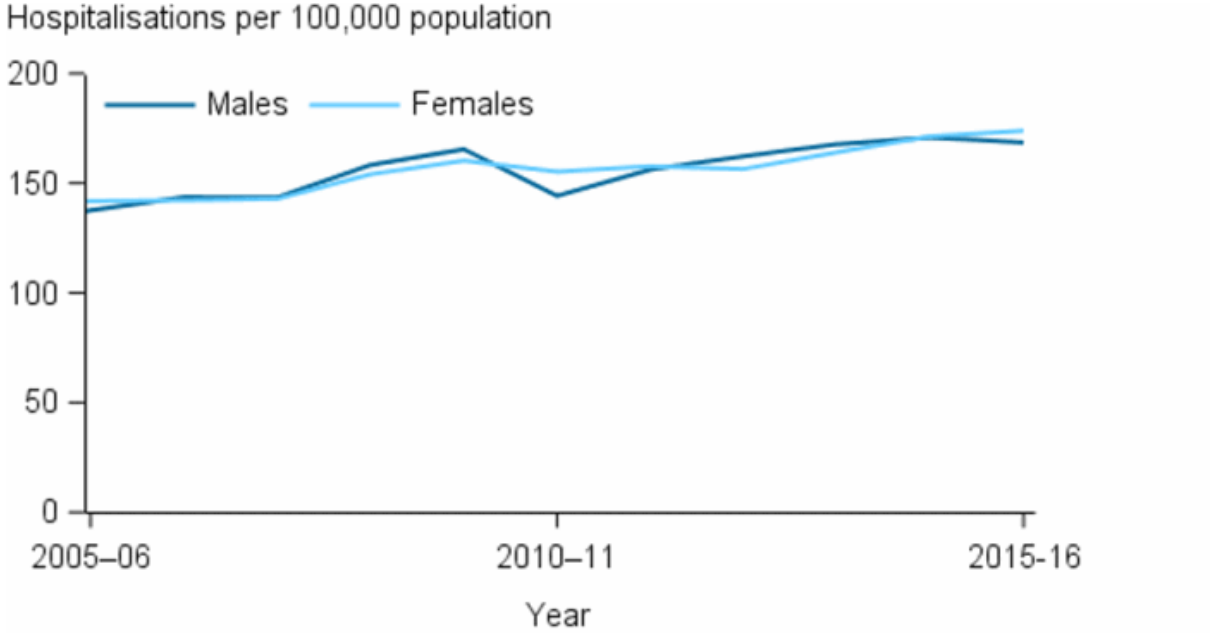


Figure 1.9. Trends of hospitalisation in Australia with CKD as a principal diagnosis (excluding dialysis) between 2005-06 to 2015-16, by gender[107]

CKD was responsible for 11% of all deaths in Australia in the year 2015, representing nearly 17,000 deaths.[107] The rates of death due to CKD, as an underlying and/or associated cause, has remained relatively stable between the year 1997 and 2015, and was responsible for almost 13,000 deaths per year during this time frame.[107] The extent of the problem can also be illustrated through the higher number of lives that CKD claims each year than prostate cancer, breast cancer, or traffic accidents.[97] Of note, CKD-related deaths are more common among males (1.5 times higher than females) and older people (4 times higher in those aged 75-84 years).[107] In Indigenous Australians, CKD contributes to 16% of all deaths. This is equivalent to 3.9 times higher risk in Indigenous females and 2.6% times higher rate for Indigenous males as compared with non-Indigenous Australians.[111]

CKD places a significant burden on the Australian economy.[112] Patients with CKD incur significantly higher total costs, including healthcare and non-healthcare costs, and governmental social benefits (excluding age-related pension), compared with age-matched Australians without CKD.[112] Further, the cumulative cost of treating existing and emerging cases of ESKD is estimated to be around AUD 12 billion for the period 2009-2020.[97]

1.2.3.7. Comorbidities and disease-related complications in CKD

Diabetes mellitus, hypertension, and other cardiovascular diseases are the most common comorbidities in patients with CKD. While more than 70% of patients with CKD have coexisting hypertension, nearly 40% have diabetes mellitus as a comorbidity.[113] Cardiovascular diseases are primarily responsible for the morbidity and mortality in these patients.[89,114] For example, patients with CKD are 20 times more likely to die from cardiovascular conditions than those without CKD.[109] Further, Australian data show that 51% of patients with CKD have cardiovascular diseases and/or diabetes as comorbidities.[109] This burden increases with age, with people aged 65 years or older being 16-45 times as likely to have concomitant cardiovascular disease, diabetes and/or CKD, compared with younger people.[109] (Figure 1.10.)

CKD is also associated with various complications that often manifest in the later phase of the disease. Anaemia and iron deficiency are among the most common complications of CKD. Anaemia in these patients occurs due to the reduction in erythropoietin production by the kidney due to the loss of renal mass and shortened red blood cell survival. The risk of developing anaemia increases with declining GFR, with around 67% of people with ESKD affected.[115]

Metabolic acidosis is another complication that is more prevalent in people with a severe form of CKD. Acidosis occurs mainly because of an increased tendency for hydrogen ion retention in patients with CKD. This complication can lead to an increased risk of proteinuria, dissolution of bone, disease progression and mortality.[116] Hyperuricaemia, fluid and electrolyte imbalances, mineral and bone disorders (primarily hyperphosphataemia), hypertension, dyslipidaemia, and sexual dysfunction are among other disease complications that occur in patients with CKD.

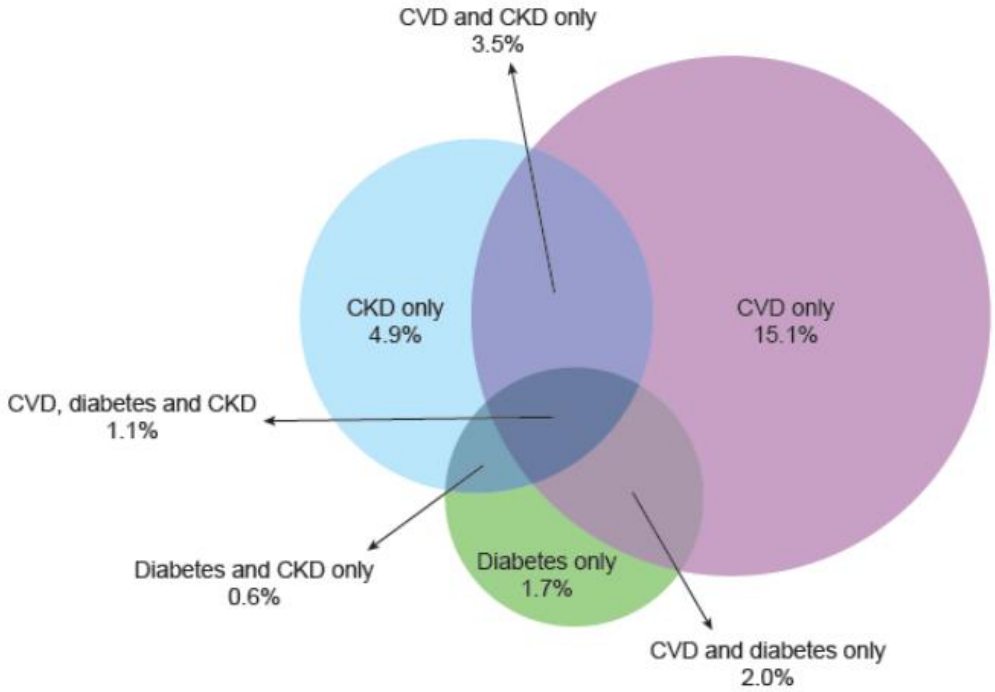


Figure 1.10. Prevalence of cardiovascular diseases (CVD), diabetes, CKD, and their comorbidity, among persons aged 18 and over in Australia, 2011–12[109]

1.2.3.8. Medication use considerations in CKD

1.2.3.8.1. Medication dosing

The renal system is responsible for the excretion of waste products, including drug metabolites and toxins, to maintain the extracellular environment for cell functioning. It is also responsible for maintenance of fluid and electrolyte balance in the body and secretion of various hormones that are involved in hemodynamic regulation. Therefore, in the event of renal impairment, some of these functions will be impaired or lost, resulting in harmful outcomes. This includes a build-up of renally-cleared medications and their metabolites when given at standard dose, leading to potential toxicity.[117]

In line with this, guidelines have proposed renal dosage adjustment recommendations based on the level of kidney function of patients. For this purpose, GFR is the primary marker used to assess the level of kidney functioning. This can be measured in patients using urine collection or can be estimated using the GFR equations as described in section 1.2.3.8.2. However, given that creatinine clearance calculated based on a 24-hour urine collection is not a better indicator of kidney function than estimated GFR (eGFR) values, different equations have been developed for routine laboratory and research purposes.[118]

1.2.3.8.2. Renal function estimation

For routine CKD staging and dosage recommendations, renal function is more easily estimated using equations than measured. The Cockcroft-Gault (CG) equation was the first equation developed and widely accepted estimation of renal function. It was developed in 1976 using 249 men with creatinine clearance (CLcr) ranging between 30 and 130 mL/min.[119] This equation uses serum creatinine for CLcr estimation considering factors like age, gender, and weight.[119] However, this equation has certain limitations. The use of an unstandardised creatinine assay from 1976 that cannot be traced to its origin is the main drawback of this equation, that limits its application for use in defining and staging kidney disease.[120] The other limitation with the use of the CG equation is the confusion regarding the varied use of actual, ideal or adjusted body weight, depending on the body mass of the individual.[120] Guidelines are also not consistent in the use of actual, adjusted or ideal body weight in drug dosing recommendations.[120]

The Modification of Diet in Renal Disease (MDRD) equation was developed to rectify some of the limitations of the CG formula.[121] This equation was developed using 1600 subjects and has improved accuracy and less bias compared with the CG equation in detecting kidney disease. Although most of the limitations of the MDRD are applicable to any creatinine-based equation, its inaccuracy at higher GFR values is its main downside.[122] This led to the development of another equation, the CKD Epidemiology Collaboration (CKD-EPI).[122] Although the CKD-EPI and MDRD equations were equally accurate in people with eGFR less than 60 mL/min/1.73m^2, the former is more applicable in diverse population groups and relatively accurate at higher eGFR values (> 60 mL/min/1.73m^2).[122] As such, the KDIGO guideline currently recommends the use of the CKD-EPI for diagnosis and classification of kidney disease unless there is a more preferable locally-validated version of this equation.[87] Both the MDRD and CKD-EPI equations report eGFR that is normalised to body surface area.

Concerns related to the varying accuracy of these equations in the detection of CKD are also applicable when used in terms of renal drug dosing.[123] Various guidelines have recommended dosage adjustment for medications based on CLcr, as compared to eGFR, because most published pharmacokinetic studies relied on CLcr in estimating renal function. However, a study by Stevens *et al* in 2009 concluded that, after comparing with the CG equation (using both actual and ideal body weight), the MDRD equation can be used for both pharmacokinetic studies and dosage adjustments.[124] The CKD-EPI, on the other hand, is currently used to report

renal function by most laboratories given its advantage over the MDRD at higher GFR values and in diverse population groups.[122] The National Kidney Disease Education Program (NKDEP)[118] suggests that unless it is for medications with a narrow therapeutic window, the interchangeable use of the CLcr or eGFR estimation equations for dosing has little difference for most patients and medications.

1.2.3.8.3. Medication regimen complexity and its sources in CKD

Patients with CKD have one of the highest medication burdens compared with most chronic diseases.[11] Pharmacotherapy approaches in patients with CKD are directed at achieving one of the following objectives: treating causes of the disease (focussing on reversible targets), preventing or slowing disease progression, and managing the CKD-related complications.[11] (Table 1). These diverse goals inevitably cause the use of multiple medications, leading to high medication regimen complexity. Dosage forms, dosing frequency and additional instructions are other attributes of medications that can complicate medication regimens in these patients. Medication regimen complexity may not be a problem in and of itself, as the use of complex regimens could be unavoidably important in some patients. However, there are instances where regimens could be inappropriately complex and thus can be targeted via interventions. This could include: the use of frequently administered medications despite the presence of long-acting alternatives; the use of parenteral dosage forms instead of orally taken medications; or instruction to break tablets while there are lower strengths. Higher medication regimen complexity quantified in consideration of these attributes has been associated with outcomes, such as hospitalisation and medication non-adherence, albeit the findings were not consistent.[20]

Table 1. Major therapeutic goals and associated considerations for the most prevalent comorbidities and complications in CKD (based on the KDIGO 2012 and KHA-CARI guidelines)[86,87]

Therapy goals	Recommendations
Slowing disease progression	
Hypertension	❖ Individualise blood pressure target based on albuminuria ❖ Use of renin-angiotensin system (RAS) blockers in diabetic and nondiabetic adults with micro or macro albuminuria
Albuminuria	❖ Use of RAS blockers
Glycaemic control	❖ Use of RAS blockers, statins, and antiplatelet therapy, where clinically indicated ❖ Use of sodium-glucose cotransporter 2 inhibitors
Management of complications	
Anaemia	❖ Use of iron supplements (depending on therapeutic goal and use of iron/erythropoietin stimulating agents) ❖ Use of erythropoietin stimulating agents (after addressing all correctable causes of anaemia)
Metabolic acidosis	❖ Use of oral serum bicarbonate when serum bicarbonate concentration is <22 mmol/L
Bone and mineral disorders	❖ Use of vitamin D supplementation if there is documented deficiency ❖ Use of bisphosphonates and phosphate binders
Management of cardiovascular conditions	
Heart failure	❖ Use of RAS blockers, beta-blockers, and diuretics, as required
Acute coronary syndrome	❖ Antiplatelets, anticoagulants, beta-blockers and RAS blockers as per the general population
Chronic coronary artery disease	❖ Antiplatelets, anticoagulants, beta-blockers and RAS blockers as per the general population ❖ Use of single antiplatelet can be used without an increased bleeding risk ❖ Risk of bleeding should be seen considering eGFR values
Lipid management	❖ Use a statin for adults aged ≥50 years if eGFR > 60mL/min/1.73m^2 ❖ Use a statin/ezetimibe for adults aged ≥50 years if eGFR < 60mL/min/1.73m^2

Cardiovascular and metabolic diseases are the main causes of morbidity and mortality in patients with CKD that require the use of highly complex medication regimens. This is because strict blood pressure and glycaemic control are important treatment objectives to improve renal and cardiovascular outcomes in these patients.[85] Greater control of blood pressure (below 130/80 mmHg), for example, is associated with maintenance of residual renal function in patients with CKD.[125] The use of renin-angiotensin system (RAS) blockers is especially beneficial in this regard, as they reduce proteinuria in both diabetic and nondiabetic patients with CKD and, therefore, slow disease progression.[85,126] Calcium channel blockers and mineralocorticoid antagonists are among other antihypertensive medications widely used in CKD with an effect on proteinuria.[126] The benefit of antihypertensive medications in decreasing proteinuria generally lies in their ability to reduce blood pressure. However, medications like RAS blockers and calcium channel blockers are thought to have an additional mechanism to reduce proteinuria, which is independent of the reduction in blood pressure.[127]

Management of hyperglycaemia and diabetes is another important treatment target in patients with CKD. According to the KDIGO, diabetes care should aim to achieve a haemoglobin A1c level of ~7% to prevent disease complications in these patients.[85] This and other main clinical targets that should be aimed to delay disease progression in patients with CKD are highlighted below in Table 2.

Table 2. Important laboratory targets in CKD management (based on the KDIGO 2012 guideline)[106]

Condition	Target values
Glycaemic control	❖ Haemoglobin A1c (HbA1c) ~ 7% to prevent or delay progression of the microvascular complications of diabetes, with higher targets for people with limited life expectancy, comorbidity or a higher hypoglycaemia risk.
Blood pressure	❖ CKD without albuminuria: ≤140/90 mm Hg ❖ CKD with albuminuria (≥30 mg/24h): ≤130/80mm Hg
Haemoglobin	❖ In non-dialysis CKD: 10-11.5 g/dL (≥100 g/L)
Metabolic acidosis	❖ Treatment should start when serum bicarbonate falls below 22mmol/L, although specific target is often unclear

In addition to treating the different comorbidities mentioned above, the management of CKD-related complications also contributes to the use of multiple medications with a variety of

dosage forms and complex instructions. These complications become more prevalent as the disease advances in stage.[85] The use of erythropoietin agonists, sodium bicarbonate, phosphate binders, lipid-lowering agents, and diuretics are among medications used to treat complications like anaemia, metabolic acidosis, bone and mineral density disorders, volume overload, hyperkalaemia and dyslipidaemia in advanced CKD.[126]

1.3. Thesis rationale

Several studies have assessed the prevalence of PIMs use and identified the type of medications commonly involved in patients with CKD.[17] Most of these studies defined medication (in)appropriateness based on a discrepancy between guideline recommendations and the actual clinical practice in relation to renally-cleared and/or nephrotoxic medications. However, patients with CKD typically have complex medication regimens that require the use of a comprehensive assessment of appropriateness considering all medications and the patient's specific characteristics. Understanding factors associated with medication inappropriateness is especially important to identify areas of medication prescribing that might need improvement.

Although CKD is characterised by the presence of multimorbidity and complex regimens, limited studies have evaluated the clinical outcomes associated with medication-related factors. For example, CKD is characterised by remarkably high rates of hospitalisation and hospital readmission—usually higher than the general population.[103] However, limited data is available on the association between medication-related factors and clinical outcomes in patients with CKD, with published works mainly focussed on those with ESKD.[12,128,129] Therefore, there is a paucity of evidence on medication-related outcomes in patients with CKD in general and in those at earlier stages of the disease in particular.

Patient-centred outcomes record patients' perceptions of their own wellbeing and functionality and are becoming increasingly relevant in outcome research and clinical practice.[130] These perceptions can take the form of views to general health status or they could relate to specific disease conditions.[130] For example, in pre-dialysis patients with CKD, these outcome measures can be important tools for prognostic assessment that inform future treatment modalities.[131] However, despite the increased recognition of patient-centred outcomes in patients with CKD, little is known about these outcome measures in pre-dialysis CKD.[131,132] Medication-related variables, such as medication count, regimen complexity and total pill burden, would be anticipated to affect patient-centred outcomes in patients with CKD. In particular, the relationship between medication-related factors and health-related quality of life (HRQOL) is relatively under-examined, with the data available limited to patients with ESKD.[23]

Finally, evaluation of the effect of the healthcare environment and the associated care in improving the quality use of medicines in patients with CKD is another area that has received little attention in the past. For example, hospitalisation presents an opportunity for healthcare professionals to re-evaluate the complex regimens in patients with CKD and rectify identified

problems. It is also an important opportunity to re-assess new risk factors in patients whose conditions have changed. Particularly, considering the now-established clinically-oriented role of pharmacists, hospitalisation provides pharmacists with an opportunity to review patients' medication regimens. However, little is known about the impact of the health care received during hospitalisation, including medication review by pharmacists, on the quality use of medicines in patients with CKD.

1.4. Aim and specific objectives of the thesis

The overarching aim of this thesis was to examine medication-related factors and associated outcomes in patients with CKD, considering prescriber, regimen, environmental and patient factors.

Specifically, the objectives of the thesis were to:

I. Summarise the evidence on the prevalence of inappropriate prescribing, associated clinical outcomes and the potential impact of interventions in CKD;
II. Measure the magnitude, and evaluate the impact of hospitalisation, on medication appropriateness in older adults with CKD;
III. Investigate the associations between medication-related factors, including regimen complexity, and hospital readmission in older adults with CKD;
IV. Investigate the associations between medication adherence and burden, and HRQOL in adults with advanced CKD not receiving RRT; and
V. Evaluate the role of pharmacist-led medication review on medication appropriateness in older adults with CKD.

1.5. Theoretical framework and thesis layout

Figure 1.11. illustrates the theoretical framework of this thesis. At the inception, the author hypothesised that different medication-related problems could occur at or be influenced by prescriber-, regimen-, environmental- or patient-level factors. The magnitude of these problems and factors driving them are explored applying retrospective and prospective study designs. The potential interaction between factors, such as medication appropriateness, regimen complexity and adherence, and health outcomes (hospital readmission and HRQOL) was explored. Finally, the effect of the healthcare service provided during hospitalisation, including medication review performed by clinical pharmacists, was explored in view of improving the quality use of medicines.

These concepts are discussed in detail in nine consecutive chapters. Chapter One presents the introduction of the thesis, containing the general thesis background, literature review and objectives of the thesis. Chapter Two presents a systematic review of inappropriate prescribing in patients with CKD across the care continuum, associated clinical outcomes and the impact of interventions. Chapter Three describes the findings of a retrospective study on the effect of hospitalisation on medication inappropriateness and factors associated with medication inappropriateness at hospital admission. Subsequently, Chapter Four and Five report results from two consecutive retrospective studies examining the association between medication-related factors, including regimen complexity, and hospital readmission in patients with CKD. Chapter Six describes the relationship among medication burden, adherence and HRQOL using a prospective cohort study. In Chapter Seven, the study reports findings of the effect of pharmacist-led medication review on medication appropriateness in hospitalised older patients with CKD. Chapter Eight, discusses the overall findings of the studies included in the thesis, followed by research limitations, practical implications and future directions. Finally, the conclusions and recommendations based on the studies is presented in Chapter Nine.

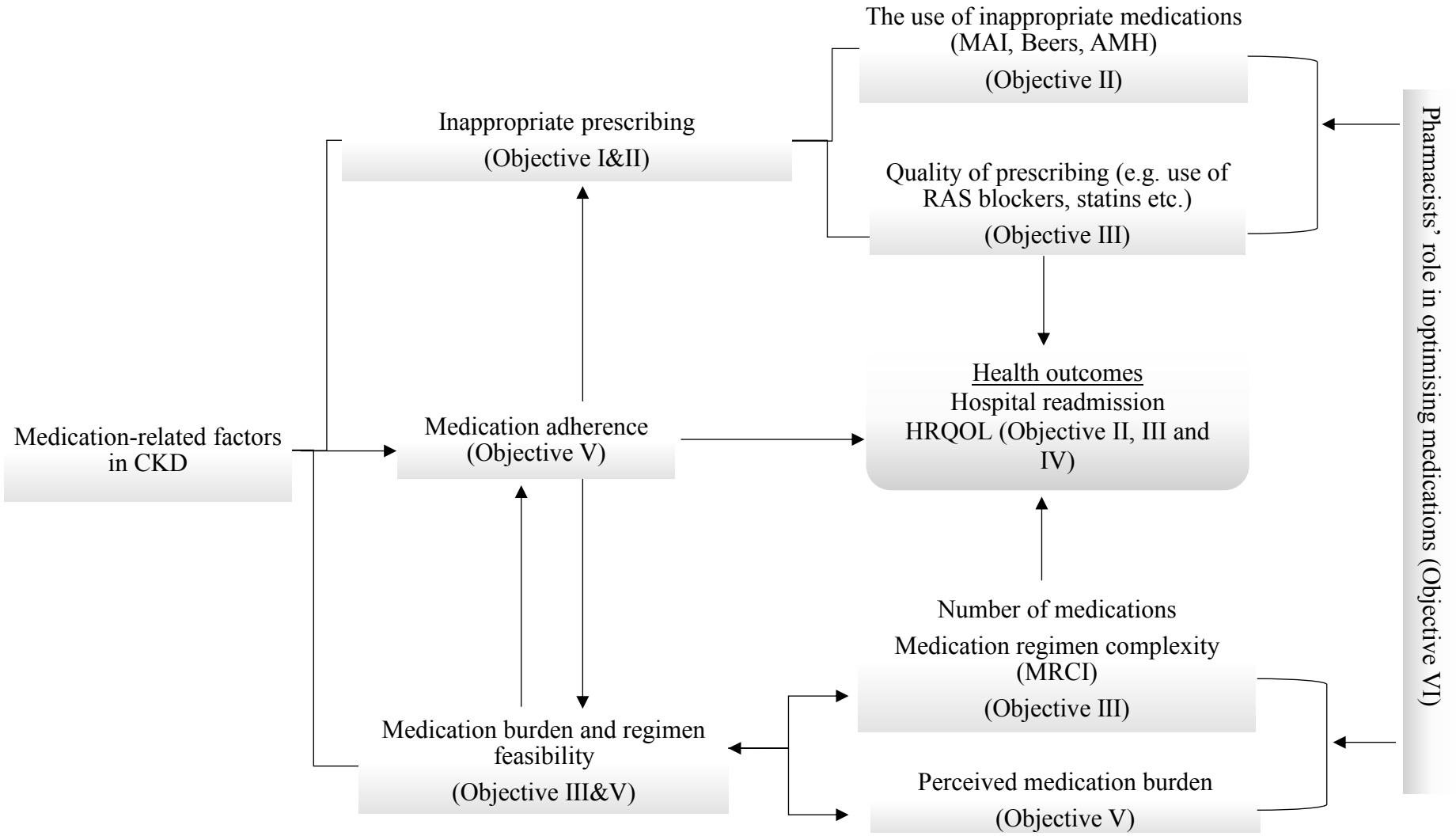


Figure 1.11. Thesis conceptual framework

(Objectives: I, Summarise the prevalence of inappropriate prescribing in CKD; II, Measure the magnitude, and evaluate the impact of hospitalisation, on medication appropriateness in CKD; III, Investigate the associations between medication-related factors and hospital readmission in CKD; IV, Investigate the interplay among medication burden, adherence and HRQOL in advanced CKD; and V, Evaluate the role of pharmacist-led medication review on medication appropriateness in CKD.)

2. CHAPTER TWO: Inappropriate prescribing in chronic kidney disease: A systematic review of prevalence, associated clinical outcomes and impact of interventions

Overview

This chapter presents a study that addresses the first objective of the thesis. It summarises the prevalence of inappropriate prescribing in patients with CKD, identifies factors and clinical outcomes associated with inappropriate prescribing and examines the effect of interventions in reducing inappropriate prescribing.

This work is a reproduction of the following publication.

Wubshet Hailu Tesfaye[1], Ronald L. Castelino[2], Barbara C. Wimmer[1] and Syed Tabish R. Zaidi.[1]

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Summary

The key finding from the systematic review above was that inappropriate use of medications was common and widespread depending on the healthcare setting and stages of disease. Further, the focus of the included studies was medications that are renally-cleared and/or nephrotoxic and, thus, should be adjusted or avoided in the event of renal impairment. However, the complex regimen used in CKD management necessitates the evaluation of medication appropriateness using robust techniques that transcend the mere checking of dosage adjustment of renally-cleared medications. Another important observation was that some medications, for example angiotensin converting enzyme inhibitors (ACEIs) and metformin, were not necessarily dose-adjusted based on renal impairment but clinical outcomes. Based on these observations, the following study was conducted to evaluate medication (in)appropriateness using a more comprehensive approach and to identify the medications involved.

3. CHAPTER THREE: The effect of hospitalisation on potentially inappropriate medication use in older adults with chronic kidney disease

Overview

This chapter presents a study addressing the second objective of the thesis. It is an evaluation of medication (in)appropriateness in older patients with CKD using the MAI and Beers criteria. These criteria are applicable in older people. Additionally, Chapter Three explores the impact of hospitalisation and the care involved on medication appropriateness in patients with CKD.

This chapter is a reproduction of the following publication.

Wubshet H. Tesfaye[a], Barbara C. Wimmer[a], Gregory M. Peterson[a,b], Ronald L. Castelino[c], Matthew D. Jose[a,d,e], Charlotte McKercher[d] and Syed Tabish R. Zaidi[a,f]

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Summary

The above study evaluated medication inappropriateness and how that is impacted by the healthcare environment. Results revealed that various medication classes, both renally-cleared and those that are excreted via other routes, are potentially prescribed inappropriately. Although hospitalisation resulted in a significant decline in medication inappropriateness, there was still space for improvement.

Interestingly, medications, such as metformin and spironolactone, are commonly prescribed inappropriately in mild to moderate stages of CKD. This could be because, as discussed in Chapter Two, clinicians use objective clinical targets (for example potassium levels) for discontinuation and/or adjustment of medications rather than solely relying on guidelines. This leads to the importance of the next chapter, which looks at the clinical outcomes associated with medication-related factors in older adults with CKD.

It is important to note here that while using the MAI in the evaluation of medication appropriateness, two components, feasibility of directions and relative expense, were removed. This was done mainly due to the difficulty involved in obtaining the necessary data to accurately assess these components. Previous research has used the same approach in using parts of the MAI.[133]

4. CHAPTER FOUR: Medication-Related Factors and Hospital Readmission in Older Adults with Chronic Kidney Disease

Overview

This chapter presents a study addressing the third objective of the thesis. In this work, the association between medication-related factors, such medication (in)appropriateness, regimen complexity and the use of selected medication classes, and 30-day and 90-day hospital readmission are examined targeting older adults with CKD.

This work is a reproduction of the following publication.

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Medication-Related Factors and Hospital Readmission in Older Adults with Chronic Kidney Disease

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Abstract: This study aimed to examine the association between medication-related factors and risk of hospital readmission in older patients with chronic kidney disease (CKD). A retrospective analysis was conducted targeting older CKD (n = 204) patients admitted to an Australian hospital. Medication appropriateness (Medication Appropriateness Index; MAI), medication regimen complexity (number of medications and Medication Regimen Complexity Index; MRCI) and use of selected medication classes were exposure variables. Outcomes were occurrence of readmission within 30 and 90 days, and time to readmission within 90 days. Logistic and Cox hazards regression were used to identify factors associated with readmission. Overall, 50 patients (24%) were readmitted within 30 days, while 81 (40%) were readmitted within 90 days. Mean time to readmission within 90 days was 66 (SD 34) days. Medication appropriateness and regimen complexity were not independently associated with 30- or 90-day hospital readmissions in older adults with CKD, whereas use of renin-angiotensin blockers was associated with reduced occurrence of 30-day (adjusted OR 0.39; 95% CI 0.19–0.79) and 90-day readmissions (adjusted OR 0.45; 95% CI 0.24–0.84) and longer time to readmission within 90 days (adjusted HR 0.52; 95% CI 0.33–0.83). This finding highlights the importance of considering the potential benefits of individual medications during medication review in older CKD patients.

Keywords: chronic kidney disease; medication appropriateness index; medication regimen complexity index; the elderly

1. Introduction

Chronic kidney disease (CKD) is associated with a substantial risk of cardiovascular-related morbidity and mortality [1]. Conversely, cardiovascular diseases are also among the primary causes of morbidity and mortality in patients with CKD [2]. Therefore, pharmacological treatment in patients with CKD is largely directed at preventing and managing these cardiovascular problems. In addition to these comorbidities, CKD-related complications, such as anaemia and bone and mineral disorders, further complicate pharmacological approaches when treating these patients.

Multimorbidity in CKD is associated with higher medication burden and poorer survival [3]. Due to comorbidities and disease complications, the use of multiple medications in patients with CKD is often unavoidable, increasing the risk of exposure to medication-related problems that can lead to adverse drug events [4]. Medication-related problems are common causes of hospitalisation, mortality, and poorer quality of life in people with CKD [4,5]. Conversely, a number of medications, including sodium bicarbonate, erythropoiesis-stimulating agents, urate-lowering therapy, renin-angiotensin system (RAS) blockers, statins, and mineralocorticoid antagonists, are associated with improved outcomes in patients with CKD [6–8]. Therefore, the suboptimal and/or inappropriate use of such medications could potentially lead to poor patient and clinical outcomes.

Most studies examining medication use and outcomes in individuals with CKD have focussed on those with end-stage kidney disease (ESKD) [5,9–11], with a lack of studies targeting patients in earlier stages of the disease. Also, while previous studies have frequently reported the prevalence and type of inappropriate medications in CKD, evidence associating medication-related factors with risk of hospitalisation remains limited [12–14]. Finally, despite the reported clinical benefit of certain classes of medications in this patient group [6], there is inadequate information on the clinical impact of using preventive medications in older adults with CKD. Therefore, we aimed to investigate the association between medication-related factors (medication appropriateness, regimen complexity and the use of selected medications) and the occurrence of hospital readmission and time to readmission in hospitalised older patients with CKD.

2. Materials and Methods

2.1. Study Design, Participants and Data Collection

A retrospective study targeting 204 older adults (≥65 years) with CKD, consecutively admitted to a tertiary care hospital in Tasmania for any cause between 1 January and 30 June 2015 [15], was conducted. Out of the 1472 eligible older adults with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, we included 204 patients who fulfilled the inclusion criteria, i.e., had a documented diagnosis of CKD or repeated eGFR values between 15–60 mL/min/1.73 m^2 reported for at least three months prior to admission and had not received any form of renal replacement therapy [16]. The eGFR values were estimated using the CKD Epidemiology Collaboration (CKD-EPI) [17] and are automatically reported along with requests for serum creatinine. Patients who stayed in hospital briefly (<24 h), with incomplete medical records and/or with acute kidney injury (AKI), alone or superimposed on CKD, were excluded. AKI was identified based on documentation (as noted in medical progress notes or discharge summaries) or a marked increase in serum creatinine (≥1.5 times the baseline value) [18]. People who were critically ill or died during the index hospitalisation were also excluded (Figure 1).

Demographic, laboratory, and clinical information for each patient was extracted using a state-wide digital medical record (DMR). Medications being used on a long-term basis, administered both regularly or as required, were recorded and coded using the Anatomical Therapeutic Classification (ATC) classification system of the World Health Organization [19]. Patient comorbidities and causes for the index admission and subsequent hospitalisations were coded using the *International Classification of Diseases*, 10th edition (ICD-10) [20].

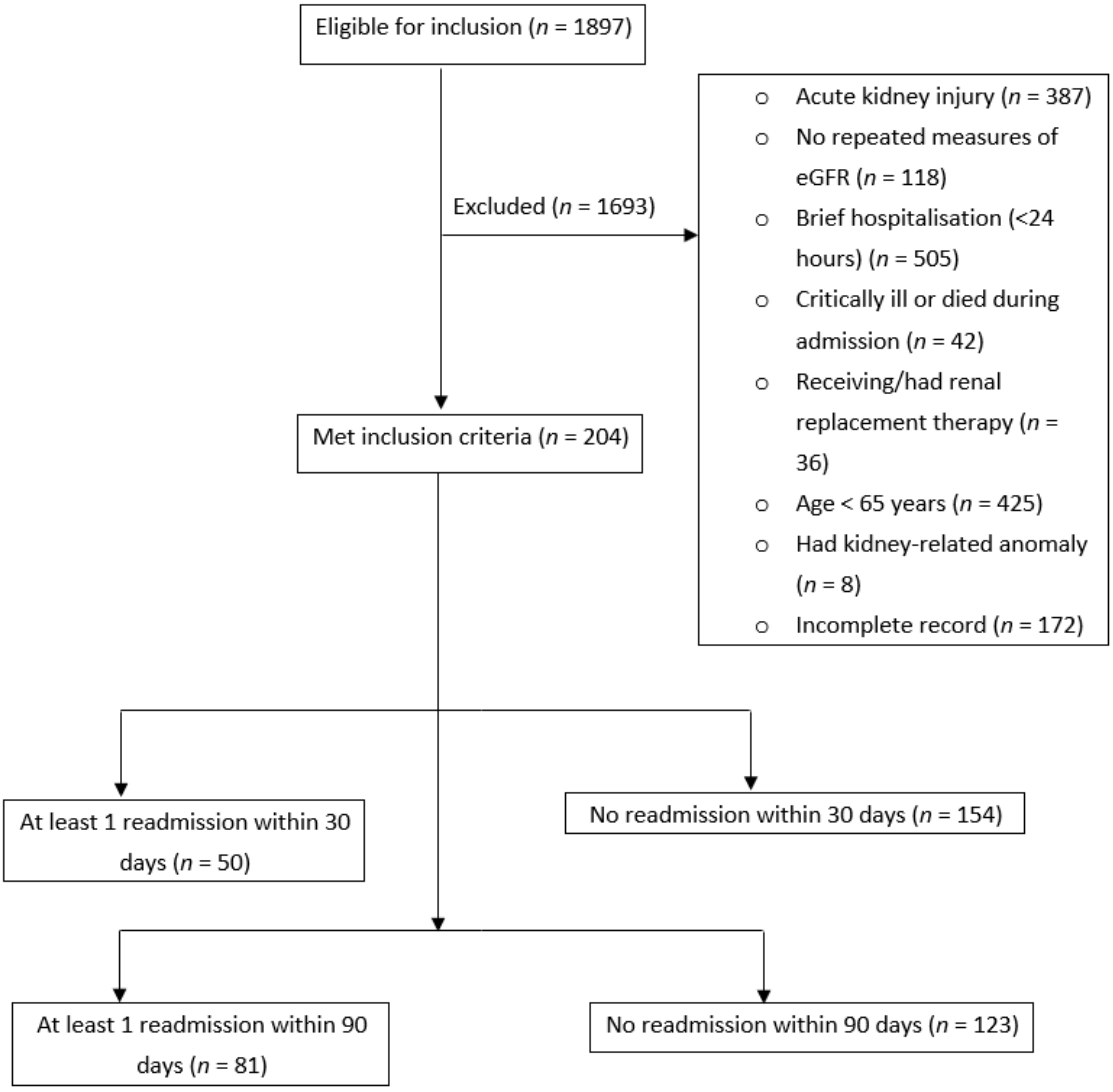

Figure 1. Flowchart of the inclusion process.

2.2. Exposure Variables

Main exposure variables were medication-related factors, including medication regimen complexity (measured using the validated Medication Regimen Complexity Index (MRCI) [21] and the number of regularly taken medications), medication appropriateness (evaluated via the Medication Appropriateness Index; MAI) [22], and the use of selected medications at hospital discharge. The MRCI is a tool that measures an individual's regimen complexity by taking into an account the dosage form, dosing frequency, and additional instructions. The MAI is an implicit measure of medication appropriateness containing 10 pharmacotherapeutic aspects: indication, effectiveness, dosage, directions and their feasibility, drug-drug and drug-disease interactions, duration, duplication and expense of medications. For practical reasons, we excluded two components of the MAI during the evaluation: the feasibility of directions and relative expense of medications [15,23]. Patient MAI scores were the summation of that of the individual medications, with higher scores reflecting a higher level of medication inappropriateness.

Given their benefit to CKD patients in general [24,25], the use of statins or RAS blockers at the index hospital discharge was included as an exposure variable in this study. Additionally, based on previous studies [6,11], the use of calcium channel blockers, beta blockers, diuretics, mineralocorticoid antagonists, and anticoagulants was also assessed during the analyses.

2.3. Outcome Variables

Outcomes of interest were (i) the occurrence of hospital readmission within 30 and 90 days of discharge and (ii) time to readmission in a 90-day follow-up period. These relatively short periods were chosen to minimise the possibility of significant changes in medication regimens of patients following their index hospitalisation.

2.4. Covariates

Renal function was measured using eGFR and serum creatinine values reported at the index hospital admission (at points closest to the date of admission). Comorbidity status was assessed at baseline using the original version of Charlson's Comorbidity Index (CCI) [26], Given the well-established link between previous hospitalisations and hospital readmission [27], the number of hospitalisations in the six months preceding the index admission was also recorded as a covariate. Socioeconomic status of patients was calculated using the Index for Relative Socioeconomic Disadvantage [28], This index considers different variables to indicate the relative disadvantage of areas, with lower scores on this index reflecting a higher proportion of relatively disadvantaged people in an area.

2.5. Analyses

Descriptive statistics were reported using means (SD) or medians (IQR) depending on the normality of data distribution, which was assessed via visual inspection of histograms. Patient, laboratory, and clinical variables were compared in patients with or without readmission during the follow-up periods. For these comparisons, chi-square tests were used to examine the differences in categorical variables between these groups. Independent samples *t*-tests and Mann-Whitney *U* tests were applied to compare continuous variables, depending on the fulfilment of the assumption of normality of distribution.

To assess the association between medication-related variables at hospital discharge and 30- and 90-day readmissions, binary logistic regression was used, with effect sizes reported as odds ratios (ORs) and 95% confidence intervals (CIs). To determine the association between the medication-related factors and time to 90-day readmission, Cox proportional hazards regression was utilised, with effect sizes reported as hazard ratios (HRs) and 95% CIs. We employed two models in the Cox regression analysis: one partially adjusted for age, gender, and CCI (Model 1) and another one fully adjusted for the factors in Model 1 plus eGFR, the number of prior hospitalisations and discharge destinations (home versus residential care). Variables were included in the multivariate models based on either a $p < 0.1$ result on unadjusted analysis or a priori based on their relevance in predicting similar outcomes in previous studies [1,11,29]. For this analysis, the end of follow-up was set at 90 days after hospital discharge or date of death, whichever occurred first. Kaplan–Meier plots were also used for visual depiction of the difference in readmission risks within 90 days based on different MAI scores (categorised into quartiles as follows: 0–2; 3–5; 6–9 and 10–29) and the use of RAS blockers. Finally, to understand if people with multiple hospitalisations were medically more complex, we examined the relationship between the number of prior hospitalisations and medication-related variables at hospital admission, with results reported using Spearman's coefficient. Analyses were performed using STATA, version 15.1 (StataCorp LLC, College Station, TX, USA). The study was conducted in accordance with the Declaration of Helsinki, and the Tasmanian Human Research Ethics Committee granted ethical approval for this study (H0016044).

3. Results

Overall, 204 older CKD patients (61% males) were included for analysis (Figure 1). Of these, 50 (24.5%) and 81 (40%) patients were readmitted at least once within 30 and 90 days of discharge from the index hospitalisation, respectively. The mean number of days to 90-day readmission was 66 (SD 34). Table 1 shows the baseline characteristics of participants. Additional laboratory and clinical information of the included patients are also presented in the attached Supplementary Material.

The most common causes of index hospitalisation were diseases of the circulatory system (41%), external causes of morbidity and mortality (e.g., fall-related) (14%) and infections (8%). Diseases of the circulatory system also contributed to more than one-third of readmissions within 30 (36%) and 90 days (36%). (Figure 2) Half of the included patients were prescribed RAS blockers (51%), with an almost equivalent number taking statins (49.5%). Similarly, while half of the patients were on diuretics, nearly a third of them were prescribed calcium channel blockers (28%) and mineralocorticoid antagonists (25%).

Patients taking RAS blockers were relatively younger (mean [SD]: 80 [8] vs. 83 [7] years; $p < 0.01$) and had diabetes as a comorbidity (63% vs. 46%; $p = 0.02$) compared to those not on these medications. Additionally, most patients on RAS blockers had no hospitalisation record in the six months preceding the index admission (65%), with only 8.5% of them having three or more prior hospitalisations. However, users of RAS blockers were not significantly different in terms of gender (male: 52% vs. 48%), CCI (median [IQR]: 4 [2–5] vs. 4 [3–5]) and eGFR (mean [SD]: 36 [11] vs. 38 [9] mL/min/1.73 m^2).

Table 1 shows that there was no significant difference in most of the medication-related variables among patients with or without hospital readmission within 30 days. MAI and MRCI were not significantly associated with the occurrence of readmission within 30 and 90 days on adjusted analyses (Table 2). However, the number of prior hospitalisations (in the six months before the index admission) significantly increased the risk of 30-day (OR 1.41 95% CI 1.05–1.90) and 90-day (OR 1.54 95% CI 1.15–2.10) readmissions after adjusting for age, gender, eGFR, CCI and the number of medications. The use of RAS blockers was associated with a reduced occurrence of readmission within both 30 (OR 0.39; 95% CI 0.19–0.79) and 90 days (OR 0.45 95% CI 0.24–0.84) after adjusting for the same variables.

Similarly, MAI and MRCI were not associated with time to 90-day readmission on fully adjusted models (Table 3). After adjusting for age, gender, CCI, eGFR and discharge destination, the number of prior hospitalisations was predictive of the timing of readmission within 90 days (HR 1.44; 95% CI 1.19–1.73). The Kaplan-Meier plots (Figure 3) illustrate that people in the highest quartile of the MAI had a relatively shorter time to readmission within 90 days compared to people in the lowest quartile (60 vs. 72 days; $p < 0.05$). The use of RAS blockers was associated with longer time to readmission within 90 days in both partially (HR 0.52 95% CI 0.33–0.83) and fully adjusted (HR 0.49; 95% CI 0.30–0.78) models (Table 3). The use of calcium channel blockers, beta blockers, diuretics, mineralocorticoid antagonists, and anticoagulants was not associated with hospital readmission in this patient group.

Finally, the number of prior hospitalisations was significantly associated with MRCI at the index hospital admission (Spearman's $r = 0.20$; $p = 0.02$). However, it was not significantly associated with the number of medications ($r = 0.14$; $p = 0.05$) or the MAI ($r = 0.10$; $p = 0.32$) at the index admission.

Table 1. Patient characteristics by 30- and 90-day readmissions.

Characteristics	Total (n = 204)	30-Day Readmission			90-Day Readmission		
		Yes (n = 50)	No (n = 154)	p	Yes (n = 81)	No (n = 123)	p
Age (years), mean (SD)	82 (7.6)	81 (7.3)	82 (7.7)	0.61	81 (7.4)	82 (7.8)	0.37
Male gender, n (%)	125 (61)	36 (72)	89 (58)	0.07	54 (67)	71 (58)	0.20
SBP (>140 mm Hg), n (%)	84 (41)	20 (40)	64 (42)	0.85	36 (44)	48 (39)	0.44
Serum creatinine (μmol/L), median (IQR)	134 (113–162)	142 (119–183)	134 (110–162)	0.11	128 (115–164)	138 (113–162)	0.16
eGFR (mL/min/1.73 m^2), mean (SD)	37 (10)	36 (12)	37 (9.6)	0.16	37 (9)	37 (11)	0.77
CCI, median (IQR)	4 (3–5)	4 (3–5)	4 (2–5)	0.35	4 (2–5)	4 (2–5)	0.17
CCI (>3), n (%)	157 (77)	41 (82)	116 (75)	0.33	68 (84)	89 (72)	0.05
No. of medications at admission, median (IQR)	10 (7–13)	10 (6–13)	10 (7–12)	0.32	10 (7–12)	9 (6–13)	0.18
No. of medications at discharge, median (IQR)	10 (7–13)	10 (7–13)	10 (7–13)	0.24	11 (7–13)	9 (6–12)	0.02
MRCI at admission, median (IQR)	25 (17–33)	28 (21–34)	24 (16–33)	0.09	27 (20–34)	23 (15–32)	0.04
MRCI at discharge, median (IQR)	27 (20–35)	30 (21–36)	26 (18–34)	0.12	30 (22–37)	26 (17–34)	0.01
MAI at admission, median (IQR)	6 (3–12)	6 (4–13)	6 (3–11)	0.49	7 (4–12)	6 (3–11)	0.08
MAI at discharge, median (IQR)	5 (2–9)	6 (3–10.5)	4.5 (2–9)	0.23	7 (2.5–12)	4 (2–8)	0.03
Use of different medications, n (%)							
RAS blockers	105 (51)	18 (36)	87 (56)	0.01	35 (43)	70 (57)	0.05
Statins	101 (49.5)	26 (52)	75 (49)	0.68	38 (47)	63 (51)	0.55
Calcium channel blockers	58 (28)	14 (28)	44 (29)	0.93	23 (28)	35 (28)	0.99
Beta blockers	94 (46)	23 (46)	71 (46)	0.99	39 (48)	55 (45)	0.63
Diuretics	104 (51)	26 (52)	78 (51)	0.87	44 (54)	60 (48)	0.44
Anticoagulants	53 (26)	11 (22)	42 (27)	0.46	18 (22)	35 (28)	0.32
Aldosterone antagonist	32 (16)	10 (20)	22 (14)	0.33	15 (18)	17 (14)	0.37
Primary cause of hospitalisation, n (%)				0.71			
Cardiovascular	80 (39.2)	22 (44)	58 (38)		35 (43)	45 (37)	0.63
Infection	25 (12.2)	6 (12)	19 (12)		9 (11)	16 (13)	
Other	99 (48.5)	22 (44)	77 (50)		37 (46)	62 (50)	
Prior admission(s) in six months before, n (%)	101 (49.5)	27 (54)	74 (48)	0.46	49 (60)	52 (42)	0.01
Discharge destination, n (%)				0.18			
Home	162 (79.4)	43 (86)	119 (77)		69 (43)	93 (57)	0.09
Residential care	42 (20.1)	7 (14)	35 (23)		12 (29)	30 (71)	
IRSD (lowest quartile)	51 (12)	14 (28)	37 (24)	0.59	22 (27)	29 (23.5)	0.68

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI, Charlson's comorbidity index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; IRSD, index of relative socioeconomic disadvantage; IU, international unit; MAI, Medication Appropriateness Index; MRCI, medication regimen complexity index; RAS, renin angiotensin system; SBP, systolic blood pressure; SD, standard deviation.

Table 2. Logistic regression for medication-related factors and occurrence of readmission within 30 and 90 days.

	Unadjusted ORs (95% CIs)	Adjusted ORs (95% CIs) ¶
a Readmission within 30 Days		
MAI	1.03 (0.97–1.09)	1.01 (0.94–1.07)
MRCI	1.21 (0.94–1.55)	1.24 (0.95–1.63)
Use of RAS blockers	0.43 (0.22–0.84)	(0.19–0.79)
b Readmission within 90 Days		
MAI	1.07 (1.01–1.12)	1.06 (1.00–1.12)
MRCI	1.33 (1.06–1.68)	1.31 (0.99–1.72)
Use of RAS blockers	0.58 (0.33–1.01)	0.45 (0.24–0.84)

Abbreviations: MAI, Medication Appropriateness Index; MRCI, medication regimen complexity index; ORs, odds ratios; RAS, renin-angiotensin system ¶ Analysis adjusted for age, gender, eGFR, Charlson's Comorbidity Index, prior admissions and the number of medications.

Table 3. Cox proportional hazards regression for medication-related factors and time to readmission within 90 days.

	Unadjusted HRs (95% CIs)	**Adjusted HRs (95% CIs)**
Model 1		
MAI	1.04 (1.01–1.08)	1.04 (1.01–1.08)
MRCI	1.18 (1.01–1.39)	1.23 (1.03–1.47)
Use of RAS blockers	0.57 (0.38–0.89)	0.52 (0.33–0.83)
Model 2		
MAI	1.04 (1.01–1.08)	1.03 (0.99–1.08)
MRCI	1.18 (1.01–1.39)	1.16 (0.96–1.39)
Use of RAS blockers	0.57 (0.38–0.89)	0.49 (0.30–0.78)

Abbreviations: HRs, hazard ratios; MAI, Medication Appropriateness Index; MRCI, medication regimen complexity index; RAS, renin-angiotensin system. Model 1: Analyses adjusted for age, gender and Charlson's Comorbidity Index. Model 2: Analyses adjusted for factors in Model 1 plus eGFR, prior admissions and discharge destination.

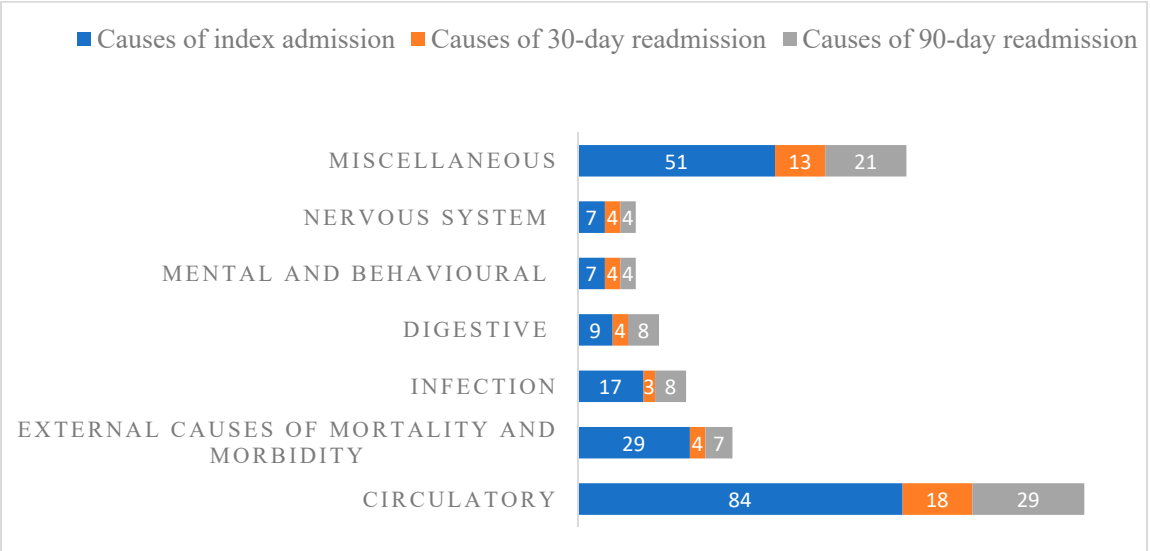

Figure 2. Causes for the index hospital admission and subsequent readmissions within 30 and 90 days, by ICD-10 classification (in frequencies).

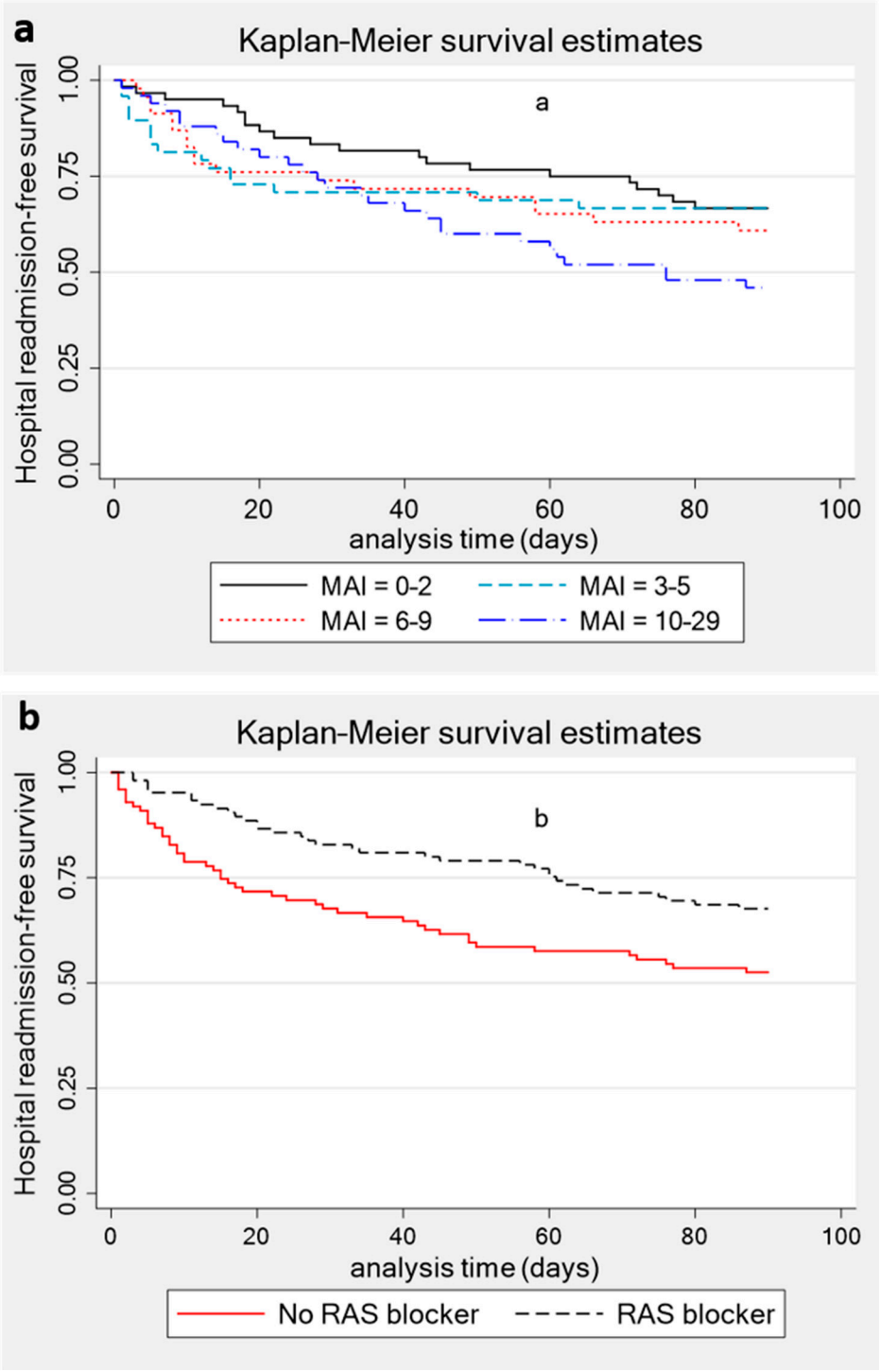

Figure 3. Kaplan-Meier hospital readmission-free survival by (**a**) quartiles of the MAI, and (**b**) the use of renin-angiotensin system (RAS) blocker.

4. Discussion

This study indicates that medication appropriateness and regimen complexity were not independent predictors of hospital readmission within 30 and 90 days in older adults with CKD. However, unadjusted results suggested that people with higher degree of medication inappropriateness and more complex regimens tended to be readmitted relatively sooner within 90 days of discharge. These findings suggest that medication inappropriateness and regimen complexity, even though not

independently associated with readmission, were likely to reflect poorer health and multimorbidity, which may have contributed to the overall readmission rate in these patients.

Previous studies have reported conflicting results regarding the relationship between medication appropriateness and hospital readmission. For example, studies reported that a greater number of medications, but not inappropriate medication use, was associated with elevated risk of hospitalisation and death [12,30], with no differences observed in people with or without CKD [12]. Furthermore, a randomised trial aimed at improving medication therapy management in CKD patients (stage 3–5; not on dialysis) after hospital discharge did not translate to a reduced occurrence of readmission within 90 days [31]. In contrast, another study targeting general older adults showed that the use of inappropriate medications (measured using explicit measures) at hospital discharge was significantly associated with repeated hospital readmissions [32].

The number of hospitalisations in the six months prior to the index admission was strongly associated with hospital readmission within 30 and 90 days. Prior hospitalisation increased the odds of 30- and 90-day readmissions by 43% and 54%, respectively, and resulted in a significantly shorter time to readmission within 90 days. The association between previous hospitalisations and risks of subsequent readmission in older adults has previously been reported [14,27,33]. It would be anticipated that people with repeated hospitalisations are likely to be sicker and medically more complex than those with less frequent hospitalisations. This probably explains the significant correlation between the number of prior hospitalisations and medication regimen complexity at hospital admission in our study. Additionally, given that each hospital admission has the potential of causing a substantial change in the medication regimen [34], multiple hospitalisations are bound to result in frequent medication regimen changes in these patients. This, in turn, may affect medication management and adherence, especially in older adults with lower cognitive functioning or social support.

An important finding from this study was the association between the use of RAS blockers and lower risk of readmission, both within 30 and 90 days. This is interesting because these medications are the first-line treatment for hypertension in diabetic and nondiabetic CKD patients, especially those with proteinuria [25,35]. These medications are also an important part of pharmacotherapy in different cardiovascular conditions and their use is associated with lower cardiovascular events in people with CKD [36,37]. It is worth noting that the main reasons for index hospitalisation and hospital readmissions in our study were cardiovascular in nature. Therefore, in addition to their role in maintaining residual renal function [38], the cardioprotective effect of these medications appears to be of great importance in terms of reducing potential cardiovascular-related admissions. Consistent with our report, a longitudinal study that followed older adults with ESKD for up to three years reported an association between use of RAS blockers and lower risk of hospitalisation [11]. However, another study targeting a small number of older patients with stage 4 and 5 CKD (mean eGFR of 16.38 mL/min/1.73 m^2) reported that the discontinuation of RAS blockers was associated with improved outcome [39]. Another large study targeting people with AKI also showed that the use of RAS blockers was linked to lower mortality but a higher risk of hospitalisation for renal causes, especially acute renal failure and hyperkalemia [40]. Of note, we found higher use of RAS blockers in the relatively younger and in those with no hospitalisation history, suggesting that these medications tended to be prescribed more commonly to relatively healthier individuals. This could be because frail individuals, such as those with frequent hospitalisations, may have a lower tolerance to the potential adverse effects of these medications, including worsening renal function, hyperkalaemia, and hypotension. While available data generally indicate the benefit of these medications in older CKD patients, the presence of proteinuria as well as the risk of progression and overall health should be considered when initiating RAS blockers [41].

Our study has some strengths and limitations. Access to data from the state-wide DMR has enabled us to accurately track patients' hospitalisation records. Admission data in this study are therefore likely to be accurate and complete. The use of validated tools to evaluate medication appropriateness and regimen complexity is another strength of the study. We evaluated the association

between medication-related factors at one point (discharge) and readmission after up to three months of follow-up. Our analysis, therefore, did not consider changes in medication regimens during the follow-up period. Finally, although we assessed the impact of medication-related factors, due to the retrospective nature of the study, we were not able to assess the level of medication adherence or ascertain the causality of the observed associations.

5. Conclusions

Medication appropriateness and regimen complexity were not independently associated with 30- and 90-day hospital readmissions in older adults with CKD. While there is a clear need for a larger prospective study, the significant association between the use of RAS blockers and reduced risk of 30- and 90-day readmissions suggests that these medications could be particularly beneficial in older adults with CKD.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/8/3/395/s1, Table S1: Additional laboratory and clinical characteristics of the included patients by readmission status (n = 204).

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Summary

The above study indicated that, despite the medical complexity in this patient group, medication regimen complexity and inappropriateness were not predictors of hospital readmission in older adults with CKD. However, the use of RAS blockers appeared to be associated with a lower risk of readmission within 30 and 90 days, highlighting the need to thoroughly assess patients' regimen considering the benefit and risk associated with individual medications. Although there was no significant association between medication-related problems and hospital readmission within 30 and 90 days, the author did not consider a change in medication regimen due to hospitalisation in the analyses.

It is important to consider that people could be readmitted due to a lack of communication during transition and lack of proper follow-up in a primary care setting. Therefore, adequate follow-up of patients after hospital discharge and performing medication reconciliation at each point across the care continuum have the potential to reduce hospital readmissions.

Following this, a subsequent study focusing on the association between medication regimen complexity and risk of readmission was assessed. This is relevant given its implication for further research and interventions targeting patients post-discharge.

5. CHAPTER FIVE: Medication Regimen Complexity and Hospital Readmission in Older Adults with Chronic Kidney Disease

Overview

This chapter expands on Chapter Four addressing the third objective of the thesis, with special focus on medication regimen complexity. It therefore examines the association between medication regimen complexity and hospital readmissions within a year of follow-up.

This chapter is a reproduction of the following publication.

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Medication Regimen Complexity and Hospital Readmission in Older Adults With Chronic Kidney Disease

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Abstract

Background: Chronic kidney disease (CKD) is characterized by high rates of hospital admissions and readmissions. However, there is a scarcity of research into medication-related factors predicting such outcomes in this patient group. **Objective**: To evaluate the effect of medication regimen complexity at hospital discharge on subsequent readmissions and their timing in older adults with CKD. **Methods**: This was a 12-month retrospective cohort study of 204 older (⩾65 years) CKD patients in an Australian tertiary care hospital. Medication regimen complexity was quantified using the 65-item medication regimen complexity index (MRCI). The outcomes were the occurrence of readmission in 30 days and time to readmission within 12 months. Logistic regression was used to identify factors predicting 30-day readmission, and a competing risks proportional subdistribution hazard model, accounting for deaths, was used for factors predicting time to readmission. **Results**: Overall, 50 (24%) patients, predominantly men (72%), were readmitted within 30 days of follow-up. MRCI was not significantly associated with 30-day readmission (odds ratio [OR] = 1.27; 95% CI = 0.94-1.73). The median (interquartile range) time to readmission within 12 months was 145 (31-365) days. On a multivariate analysis, a 10-unit increase in MRCI was associated with a shorter time to readmission within 12 months (subdistribution HR = 1.18; 95% CI = 1.01-1.36). **Conclusion and Relevance**: Medication regimen complexity was not significantly associated with 30-day readmission; however, it was associated with a significantly shorter time to 12-month readmission in older CKD patients. This finding highlights the importance of medication regimen complexity as a potential target for medical interventions to reduce readmission risks.

Keywords

chronic kidney disease, elderly, hospital readmission, medication regimen complexity, predictors

Introduction

Medication-related problems are important causes of adverse health outcomes, including hospitalizations and readmissions.[1,2] Hospital readmission is considered a service quality metric that may indicate poor inpatient care.[3] Although the estimates vary considerably, studies have found that hospital readmissions related to medications are common, and many of these readmissions are considered preventable.[4] Medication regimen complexity is a modifiable risk factor that is associated with poor adherence and hospital readmissions in older adults.[5-10] Despite this, evidence on the association between medication regimen complexity and clinical outcomes is equivocal.[8] The multiple changes that occur during hospitalization have been associated with increased medication regimen complexity.[11] It has also been reported that when hospitalization-led medication changes are followed by inadequate medication reconciliation and follow-up, they can increase patients' risk of hospital readmission.[12-14]

Older adults with chronic kidney disease (CKD) are among patient groups with highly complex drug regimens

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and, therefore, potentially at increased risk of medication-related hospitalizations.[2] CKD patients also have higher rates of hospitalizations and hospital readmissions than those without CKD,[12,15] although research into the modifiable causes of hospitalizations in these patients remains scant.[12] Identifying modifiable risk factors that can be used clinically in identifying patients at risk of future readmissions is imperative in designing and implementing pragmatic preventive strategies.

Despite CKD patients' greater risk of hospital admissions and readmissions, the role that medication regimen complexity plays in predicting such outcomes has not been investigated. Furthermore, there is a relative paucity of medication-related outcome data in people with CKD. Therefore, we aimed to examine the association between medication regimen complexity at hospital discharge and readmission within 30 days in older CKD patients. Moreover, we aimed to determine the association between medication regimen complexity and time to hospital readmission in a 12-month follow-up period.

Methodology

Study Design and Participants

This was a 12-month retrospective cohort study conducted in a 500-bed tertiary care hospital in Tasmania, Australia. Older patients (aged ⩾65 years) with CKD (estimated glomerular filtration rate [eGFR] of 15-60 mL/min/1.73m^2), estimated via the CKD epidemiology collaboration (CKD-EPI) equation,[16] at a point closest to discharge and who were hospitalized between January and June 2015 were eligible for inclusion. Of 1472 older adults with at least 1 low eGFR value reported and who were hospitalized during the study period, 204 met the inclusion criteria. Patients were excluded for one of the following reasons: (1) stayed for a period shorter than 24 hours (n = 505), (2) had acute kidney injury (n = 387), (3) were critically ill/died during admission (n = 42), (4) had no repeated measures of eGFR over a period longer than 3 months to confirm CKD (n = 118), (5) receiving renal replacement therapy (n = 36), (6) had anomalies (n = 8), and (7) had incomplete records (n = 172). The study was approved by the Tasmanian Human Research Ethics Committee (H0016044).

Data Collection

Demographic, laboratory, and medical information for participants was extracted from their medical records. The Anatomical Therapeutic Chemical classification system[17] was used to record and classify medications, whereas the *International Classification of Diseases* (ICD-10)[18] was used to code the reasons for hospital readmission. A list of patients with low eGFR (<60 mL/min/1.73m^2) values reported between January and June 2015 were electronically extracted using patient identifiers from Royal Hobart Hospital Pathology. Using the digital medical record (DMR) of the Department of Health and Human Services, each patient was evaluated for inclusion based on the predefined criteria. The discharge summaries of patients who met the inclusion criteria were thoroughly reviewed by the principal investigator (WHT) to retrieve drug information, including dosage form, dosing frequency, and additional instructions, which formed the basis to calculate the discharge medication regimen complexity.

Measures

Medication regimen complexity was the main exposure variable and was quantified using the 65-item medication regimen complexity index (MRCI).[19] The MRCI comprises dosage forms, dosing frequency, and additional directions, with each component assigned different weights. The total MRCI is the sum of the scores for the 3 sections, and higher scores reflect more complex medication regimens. This score has no upper limit because there is no limit to the number of medications that could be prescribed to a patient or additional directions given.[19] Typically, a medication that has to be administered twice daily receives a higher score than once-daily dosing. Parenteral and inhalational dosage forms receive higher scores than orally administered medications. In computing the MRCI, both regular and "as needed" medications and supplements were considered. Medications used only for a short period, including oral antibiotics and analgesics prescribed during a patient's hospital stay, were excluded from the calculation. The number of medications comprised the total sum of individual medications and supplements taken by an individual. Combination medications were counted as single medications for computing both the MRCI and number of medications.

Outcomes of interest were (1) hospital readmission in a 30-day period of discharge from the index hospitalization and (2) time to hospital readmission within 12 months. The index hospitalization was set as the first hospital admission during the study period (between January 1, 2015, and June 30, 2015) and the follow-up time of patients determined individually based on their respective discharge dates. The admission and discharge dates for the index hospitalization, readmissions during the follow-up periods, and time to the first readmission were extracted from the DMR. The follow-up data were included for people who were readmitted to the same tertiary care hospital, which is the only one in the region.

Covariates

Age, gender, the source of index hospitalization (home or residential care), the presence of hospitalizations within a

year prior to the index hospitalization, dose administration aids (DAAs) use (mainly dosette boxes and blister packs), and discharge destination were recorded. Length of hospitalization for the index admission was computed using the days between initial admission and discharge. The Charlson comorbidity index (CCI)[20] was used to determine comorbidity. We also included an examination of anticholinergic drug use, given consistent reports of an association between anticholinergic burden and both hospitalization and falls in older individuals.[21] The use of anticholinergic drugs at discharge was determined based on the use of any drug from the modified Anticholinergic Risk Scale (mARS).[22] The mARS ranks medications with anticholinergic property using a 3-point scale. The mARS score for a patient is the sum of each medication with anticholinergic effect. Socioeconomic status was determined using the Index of Relative Socioeconomic Disadvantage (IRSD) from the Socio-Economic Indexes for Areas (SEIFA 2011).[23] Using the postcode of residence, this index measures the relative level of socioeconomic disadvantage based on a range of census characteristics that reflect disadvantage, such as low income, low educational attainment, high unemployment, and jobs in relatively unskilled occupations.

Statistical Analyses

Demographics, comorbidity, and eGFR for patients with and without readmission were compared descriptively. Continuous outcomes were reported as means (SD) for normally distributed variables and medians (interquartile range [IQR]) for nonnormally distributed variables. Categorical variables were compared between readmission and nonreadmission groups using χ^2 tests; independent-samples *t*-tests were used for normally distributed continuous variables and Mann-Whitney *U* tests for nonnormally distributed continuous variables.

To evaluate factors associated with hospital readmission in a 30-day follow-up period, unadjusted and adjusted odds ratios (ORs) with 95% CIs were estimated using logistic regression. For these analyses, the number of medications and MRCI were dealt with separately because of the high correlation between the 2 variables.[7] The MRCI score was used in the analysis in tenth units (total MRCI divided by 10) because a 10-unit increase was deemed more clinically relevant and meaningful.[24] For factors associated with time to readmission in a 12-month period, a competing risks proportional subdistribution hazards model was applied to report unadjusted and adjusted subdistribution hazard ratios (HRs) and 95% CIs, as proposed by Fine and Gray.[25] We used this model because death, as a competing risk, can hinder the occurrence of readmission and, therefore, affect the relationship between MRCI and readmission. In both models, factors with a *P* value <0.20 in univariate analyses were included in the multivariate analyses. The significance level for all analyses was set at a *P* value <0.05, and data were analyzed using STATA, version 15 (StataCorp LLC, TX).

Results

A total of 204 older adults with CKD (eGFR = 15-60 mL/min/1.73 m^2) met the inclusion criteria. Their baseline characteristics are presented in Table 1. Overall, 2056 medications were prescribed at the discharge of the index hospitalization; most of these medications were orally administered (tablet and capsules; 86%) followed by inhalational (6.1%) and parenteral (4.1%) dosage forms. Paracetamol (6.3%), furosemide (5%), acetylsalicylic acid (4.7%), cholecalciferol (4.1%), and esomeprazole (3.1%) constituted the most frequently prescribed individual medications at discharge. A total of 76 (37%) patients were taking drugs with anticholinergic activity, with 26 (13%) on at least 1 very strong anticholinergic drug (mARS $\geqslant$ 3).

The median (IQR) MRCI score at discharge from index hospitalization was 27 (20-35), and the mean (SD) number of medications was 10 (4). Overall, looking at individual components of the MRCI, dosing frequency contributed to nearly half (46%) of the overall MRCI score, with a median (IQR) value of 12.4 (8-16.5).

Almost a quarter of the patients (50; 24.5%) were readmitted in the 30-day follow-up, whereas almost two-thirds of the patients (127; 62.3%) had a readmission in the 12-month period. Of included patients, 50 of them, predominantly male (68%), died before the end of the 12-month follow-up. The main reasons for readmission in the 30-day follow-up (Table 2) included cardiovascular conditions (34%), falls (10%), and infections (10%). Additionally, although 14% of the readmissions in this period were recorded as being drug induced, all patients readmitted because of falls were also taking at least 1 medication that could cause a fall. The common causes for readmission within a 12-month period were very similar to those for readmission within 30 days: cardiovascular causes (31.5%), followed by infections (14.2%) and falls (12%).

Factors Associated With Hospital Readmissions

There was no significant difference in the demographic or clinical characteristics of patients with or without readmission in the 30-day follow-up (Table 1). The number of medications (OR = 1.03; 95% CI = 0.94-1.12) and MRCI (OR = 1.16; 95% CI = 0.86-1.57) were not associated with a 30-day hospital readmission on multivariate logistic regression (Table 3).

The median (IQR) time to first hospital readmission was 145 days (31-365). On univariate analysis, MRCI was significantly associated with time to readmission in 12 months (subdistribution HR = 1.21; 95% CI

Table 1. Characteristics of Patients for the Index Hospitalization.[a]

Variables	Overall (n = 204)	Readmission Within 30 days		
		Yes (n = 50)	No (n = 154)	Significance
Age (years)	83 (76-87)	83 (77-86)	83 (76-87)	0.69
Male gender	125 (61)	36 (72)	89 (58)	0.09
Serum creatinine (μmol/L)	129 (108-162)	133 (113-174)	127 (106-127)	0.13
eGFR (mL/min/1.73 m^2)	38 (11)	38 (12)	39 (11)	0.55
Hemoglobin (g/L)	118 (106-134)	118 (103-133)	119 (108-134)	0.55
CCI	4 (3-5)	4 (3-5)	4 (3-5)	0.17
DAA	76 (37)	18 (36)	58 (38)	0.87
Length of hospitalization (days)	4 (2-8)	4 (2-8)	4 (3-8)	0.37
Regular medications	9 (4)	9 (4)	9 (4)	0.28
Total medications	10 (4)	11 (4)	10 (4)	0.27
MRCI	27 (20-35)	30 (21-37)	27 (18-34)	0.12
Anticholinergic use (⩾1 drug with mARS ⩾1)	76 (37)	23 (46)	53 (34)	0.09
Admitted from home	185 (91)	47 (94)	138 (90)	0.42
Discharged home	162 (79)	43 (86)	119 (77)	0.23
Prior admissions in 12 months (⩾2)	93 (46)	27 (54)	66 (43)	0.19
Living alone	54 (26)	12 (24)	42 (27)	0.71
IRSD (highest quartile)	46 (23)	8 (16)	38 (25)	0.59

Abbreviations: CCI, Charlson comorbidity index; DAA, dose administration aid; eGFR, estimated glomerular filtration rate; IRSD, index of relative socioeconomic disadvantage; mARS, the modified Anticholinergic Risk Scale; MRCI, medication regimen complexity index.
[a]Results are given as median (interquartile range), mean (SD), or number (percentage).

Table 2. Reasons for Hospital Readmission in 30-Day and 12-Month Follow-up Periods.

Readmission Causes	ICD-10 Codes	30 Days, n (%)[a]	12 Months, n (%)[b]
Cardiovascular	BA5Z, I20.0, I21.0, I20.8, I20.9, I25.3, I35.0, I42.0, I48.1, I49, I50.0, I50.1, I51.9, I95.2, R06.0, R55	17 (34)	41 (32.2)
Fall related	S00.0, S40.0, S82.0, S17.8, W01, W05, W06, W08, W13, W19	5 (10)	15 (12)
Infections	A09.0, A41.9, J13, J22, L03, I69.0, J00, K57.9, K61.3, N39.0, T81.4	5 (10)	18 (14.2)
Gastrointestinal	A01, K57, K61.3, K92.2, K40, K40.1, K45, K56.6, R10.1	3 (6)	9 (7.1)
Drug induced	E16.0, G50.8, R00.1, K92.2, W18	7 (14)	8 (6.3)
Miscellaneous	D01.5, E61.1, F00.9, F05.9, G41.0, H25, J44, K56.6, K81.1, K85.9, L03.1, M54.9, M86, N17.9, R10.1, R30, R10.0, H81.4, X84	13 (26)	36 (28.3)

[a]The denominator is the number of patients hospitalized within 30 days (n = 50).
[b]The denominator is the number of patients hospitalized within 12 months (n = 127).

= 1.07-1.37). Similarly, after adjusting for age, serum creatinine, CCI, anticholinergic drug use, discharge destination, IRSD, the use of DAAs, and previous admissions, higher MRCI score was associated with a shorter time to readmission (subdistribution HR = 1.18; 95% CI = 1.01-1.36). Adjusting for similar covariates, the number of medications was not associated with time to readmission in this period (subdistribution HR = 1.04; 95% CI = 0.99-1.08). On the other hand, having multiple admissions in the 12 months prior to the index hospitalization was associated with a shorter time to readmission within 12 months (adjusted subdistribution HR = 2.24, 95% CI = 1.48-3.40; Table 4). Finally, the serum creatinine of patients was weakly associated with time to readmission (adjusted subdistribution HR = 1.003; 95% CI = 1.00-1.01).

Table 3. Factors Associated With Hospital Readmission Within 30 Days After Discharge for the Index Hospitalization.

Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
MRCI	1.21 (0.94-1.55)	1.16 (0.86-1.57)
Male gender	1.88 (0.94-3.76)	1.76 (0.85-3.62)
Serum creatinine	0.99 (0.96-1.02)	0.98 (0.95-1.01)
CCI	1.25 (0.63-2.51)	1.08 (0.90-1.30)
Anticholinergic use	1.62 (0.85-3.10)	1.06 (0.83-1.36)
Prior admissions in 12 months (⩾2)	1.89 (0.92-3.87)	1.79 (0.84-3.80)

Abbreviations: CCI, Charlson comorbidity index; MRCI, medication regimen complexity index (analyzed using the tenth of the original score); OR, odds ratio.

Table 4. Factors Associated With Time to Readmission Within 12 Months.[a]

Variables	Unadjusted HRs (95% CIs)	Adjusted HRs (95% CIs)
MRCI	1.21 (1.07-1.37)	1.18 (1.01-1.36)
Age (years)	0.98 (0.96-1.00)	1.00 (0.97-1.03)
CCI	1.06 (0.98-1.14)	1.02 (0.93-1.11)
DAAs use	1.28 (0.90-1.81)	1.08 (0.73-1.60)
Discharged home	1.56 (0.95-2.55)	1.54 (0.89-2.68)
IRSD (highest quartile)	0.72 (0.44-1.17)	0.82 (0.49-1.39)
Anticholinergic use	1.09 (0.97-1.23)	1.00 (0.88-1.14)
Prior admissions in 12 months (⩾2)	2.49 (1.67-3.71)	2.24 (1.48-3.40)
Serum creatinine	1.00 (0.99-1.01)	1.003 (1.00-1.01)

Abbreviations: CCI, Charlson comorbidity index; DAAs, dose administration aids; HR, hazard ratio; IRSD, index of relative socioeconomic disadvantage; MRCI, medication regimen complexity index (analyzed using the tenth of the original score).
[a]Fine and Gray's competing risks regression model was used to compute the subdistribution HRs and 95% CIs for factors associated with readmission accounting for death as a competing factor.

Discussion

This is the first study to evaluate the association between medication regimen complexity and hospital readmission in older CKD patients. The main findings indicate that in this study, increased medication regimen complexity was associated with a significantly shorter time to 12-month readmission. Increased medication regimen complexity was also associated with an increase in the odds for 30-day readmission; however, this was not statistically significant.

Although medication regimen complexity and the number of medications were not associated with readmission within 30 days, up to 14% of these readmissions were recorded as drug induced. Furthermore, all patients who were readmitted because of a fall within this period were taking at least 1 medication that increases the risk of falls. This result suggests that individual medications are important contributors to readmission, irrespective of medication regimen complexity. This is supported by previous research indicating that taking certain drugs could predispose patients to higher risks of hospitalization, rather than the presence of polypharmacy.[26]

The association between medication regimen complexity and readmission is important because this variable has been suggested for use to target individuals at high risk of hospitalization.[27] Previous studies reported that medication regimen complexity was associated with hospital admissions and readmissions.[5-7,10] However, in most of these studies, medication regimen complexity was not identified to be a better predictor of hospitalization than the number of medications. In contrast, in our study, medication regimen complexity, but not the number of medications, was associated with time to readmission. This could be because CKD is typically characterized by the use of medications with complex instructions for treating various comorbidities and disease complications.[2] Nevertheless, compared with simply using the number of medications, computing MRCI for an individual patient is difficult to implement in routine clinical practice. However, a study showed that MRCI scores can be automatically computed and integrated into electronic health records for easier clinical decision making.[28]

The effect of medication regimen complexity on readmission has an important clinical implication because this variable, unlike simple medication count, has different components that can be targeted during medication review to optimize medication adherence. In particular, given that dosing frequency contributed the most to the overall MRCI score of patients in this study, health professionals should

consider this factor during prescribing for older adults with CKD. The use of longer-acting medications is one of the suggested strategies to reduce dosing frequency and, therefore, simplify patients' regimens.[27] This finding is particularly relevant for people who are discharged home, have lower cognitive functioning, and have little support in medication management.

Patient factors, comorbidity, number of prior hospitalizations, and length of hospitalization were some of the factors that previously predicted hospital readmission in people with CKD.[12,29] In our study, patients readmitted in 30 days were not significantly different in terms of age, comorbidity, and length of hospital stay as compared with those who were not readmitted in this period. However, although the difference was not statistically significant, patients with a 30-day readmission were more likely to be men (72%). This corresponds with the report by the Australian Institute of Health and Welfare that male CKD patients have higher hospitalization rates than female patients.[30] On the other hand, having multiple prior hospitalizations in the year preceding the index hospitalization was associated with a shorter time to readmission in the subsequent 12 months.

The use of a validated measure to compute medication regimen complexity is one strength of the study. This tool comprises important components such as dosage form, the frequency of administration, and additional instructions provided to patients. The study is limited by a relatively small sample size from a single hospital. Despite the inclusion of several factors in our analyses, we may have also missed important contributors given the complexity surrounding causes of hospital readmission. Another potential limitation was that we examined the association between medication regimen complexity at only one point and the risk of readmissions in up to 12 months of follow-up. However, the care patients receive from multiple health care providers during the follow-up period may result in changes in medication regimen complexity. Because of the retrospective nature of the study, we were unable to assess adherence to medications. The appropriateness of individual medications was also not assessed in this study; however, we have included the use of anticholinergics in our analyses, given their contribution to hospitalization in older people.[21]

Conclusion and Relevance

This study demonstrated that medication regimen complexity was not significantly associated with hospital readmission within 30 days in older patients with CKD; however, it was associated with a significantly shorter time to 12-month readmission. Although there is a need for large-scale studies to determine the relationship between medication regimen complexity and clinical outcomes in these patients, the finding highlights the importance of considering regimen complexity during medication review at hospital discharge to reduce the risk of readmission. Future studies should examine the relationship between changes in medication regimen complexity during hospitalization and risks of hospital readmissions.

Authors' Note

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Declaration of Conflicting Interests

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Summary

The study above indicates that medication regimen complexity is potentially relevant in predicting long-term clinical outcomes. This reaffirms the assertion in Chapter Five that medication regimen complexity is likely an indirect measure of overall health and morbidity status in older patients with CKD.

In the next chapter, the relevance of medication-related factors in CKD is further assessed using a cohort of adults with advanced CKD (not receiving RRT) followed prospectively for over 12 months.

6. CHAPTER SIX: Medication adherence, burden and health-related quality of life in adults with pre-dialysis chronic kidney disease: a prospective cohort study

Overview

This study addresses the fourth objective of this thesis. It is a prospective cohort study examining the relationships between medication burden and adherence, and HRQOL in adults with advanced CKD not receiving renal replacement therapy. Participants were interviewed at two points to assess the change in HRQOL over time and how medication (non)-adherence relates to such change.

This work is currently under review in the journal 'Nephrology'.

Medication adherence, burden and health-related quality of life in adults with pre-dialysis chronic kidney disease: a prospective cohort study

Abstract

Objective: To examine the associations between medication adherence and burden, and health-related quality of life in adults with pre-dialysis chronic kidney disease (CKD).

Methods: A prospective study targeting adults (≥18 years) with advanced CKD (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2) and not receiving renal replacement therapy was conducted in Tasmania, Australia. Actual medication burden was assessed using the 65-item Medication Regimen Complexity Index and a medication count, whereas perceived burden was self-reported using a brief validated questionnaire. Medication adherence was assessed using the 4-item Morisky-Green-Levine Scale (MGLS) and the Tool for Adherence Behaviour Screening (TABS). The Kidney Disease and Quality of Life Short-Form, which contains kidney disease-targeted and generic components, was used to assess health-related quality of life. Activities of daily living, cognitive functioning and autonomy preference (in decision-making and information-seeking) were among covariates assessed.

Results: Of 464 eligible adults identified and invited, 101 participated in the baseline interview and 63 completed a follow-up interview at around 14 months. Participants were predominantly men (67%), with a mean age of 72 (SD 11) years and eGFR of 21 (SD 6) mL/min/1.73m^2. While the mean number of medications was 8.5 (SD 3.7), medication non-adherence was reported in 43% and 60% of participants based on MGLS and TABS, respectively. Higher perceived medication burden (OR 4.89; 95% CI 1.02-23.5) and desire for decision-making (OR 4.56 95% CI 1.68-12.35) were associated with non-adherent behaviour. Poorer health-related quality of life was associated with higher regimen complexity, whereas medication non-adherence was associated with a decline in physical health-related quality of life over time.

Conclusion: Medication non-adherence, influenced by perceived medication burden, is prevalent in this pre-dialysis CKD cohort, and is associated with a significant decline in physical health-related quality of life even over a short time period.

Key words: Chronic kidney disease; medication adherence; health-related quality of life; Medication Regimen Complexity Index; medication burden.

Introduction

Medication adherence is the primary determinant of treatment success, yet nearly half of people with chronic conditions do not take their medications as prescribed.[21] The reported prevalence of medication non-adherence in chronic kidney disease (CKD) varies considerably; 12%-53% in stage 3 to 4 CKD and 21%-74% in end-stage kidney disease (ESKD).[134-136] Medication adherence is particularly relevant in people with CKD given its potential importance in slowing disease progression and thus improving health outcomes. Poor adherence to antihypertensive medications in CKD, reported in nearly one-third of patients, is associated with uncontrolled hypertension.[137,138] Research also indicates that non-adherence to cardiovascular medications at the pre-dialysis stage is an independent predictor of post-dialysis mortality in people with advanced CKD.[139]

Patient-centred outcomes, such as health-related quality of life (HRQOL), are important measures that capture patients' perspectives and experiences about their functionality and wellbeing.[130] These outcome measures are particularly relevant in patients with advanced CKD as they inform treatment goals and modalities.[131] Nevertheless, there is limited data on patient-centred outcomes in people with advanced CKD,[25,131,140] particularly in those not receiving renal replacement therapy.[132] More importantly, the relationship between HRQOL and medication-related factors, such as medication burden and adherence, is relatively under-examined in this patient group.[141]

Actual and perceived medication burden can be assessed in different ways including the complexity of medication regimens and the number of medications used. Medication regimen complexity and the number of medications would be expected to influence adherence, although findings on this subject are not consistent.[20] In patients with CKD, the association between medication regimen complexity and adherence is inconclusive.[25,140] Moreover, despite the high medication burden in patients with advanced CKD, evidence is lacking on the association between medication-related factors and patient-centred outcomes in pre-dialysis CKD.

This study aimed to (i) identify factors associated with medication burden (perceived and actual), (ii) examine the association between medication burden (actual and perceived) and adherence in adults with pre-dialysis CKD, (iii) examine the association between HRQOL and actual medication burden, and (iv) evaluate the relationship between medication adherence and a change in HRQOL over time.

Materials and Methods

Study design and population

This analysis utilised data from the Tasmanian CKD study, a prospective cohort of adults aged ≥18 years with advanced CKD (based on a single estimated glomerular filtration rate (eGFR) reading of <30mL/min/1.73m^2 in the 3 months prior to recruitment) and not receiving renal replacement therapy. A detailed description of the rationale, design and results of the pilot study have been published previously.[142] Participants were recruited and attended a baseline clinic between February 2016 and September 2018. Individuals with at least one medication and who agreed to participate in an additional medication interview were included in the current analysis.

At baseline, participants attended a study clinic where a range of sociodemographic, clinical, and HRQOL information was collected. Consenting participants were then contacted by a research pharmacist (WHT) to arrange an additional interview regarding participants' medications and medication-taking behaviour. At follow-up (at least a year after the baseline assessment), participants attended a clinic for an additional interview (between August 2017 and October 2018). This study was approved by the Tasmanian Health and Medical Human Research Ethics Committee (H0015099).

Measures

Medication-related factors

Medication-related information collected from participants during the baseline interview was verified using electronic health records. To determine actual medication burden, the validated 65-item medication regimen complexity index (MRCI)[18] and simple medication count were used. Perceived burden of medication (PBM), a tool previously developed and validated in adults with ESKD, was used to assess participants' perceived burden of their medication regimens.[25] This tool consists of six Likert-scale questions asking if patients feel bothered by the number of medications they take, size of pills, adverse effects of medications, the dosing frequency, the need to take medications at work or in social contexts, and the need to drink fluid to take medications.

Medication adherence was self-reported by participants at baseline using the Morisky-Green-Levine Scale (MGLS).[143] This scale consists of four questions with 'yes/no' answers, with patients deemed non-adherent if they respond 'yes' on at least one of the questions. The Tool for Adherence Behaviour Screening (TABS), a questionnaire developed in Australia to assess

adherence behaviour in adults taking chronic medications,[144] was also used during the interview. This tool has two subcomponents, one for 'adherence' and one for 'nonadherence.' The subcomponents have four items each and a differential score (i.e. total for 'adherence' minus total for 'nonadherence') of ≥15 reflects good adherence and a score of ≤14 indicates suboptimal adherence.[145] These adherence measures were chosen in this study because they address both intentional and unintentional non-adherence behaviour.

Covariates

Patient characteristics, including age, gender, marital status, level of education and means of income, and smoking history (current/former vs never), were recorded at baseline. Index of Socioeconomic Disadvantage was retrieved using the postcode of participants from the Socio-Economic Indexes for Areas of the Australian Bureau of Statistics.[146] The modified Charlson's Comorbidity Index (CCI),[147] calculated using medical conditions as reported by the participant's treating physician, was used to determine the medical comorbidities. Baseline laboratory values, including haemoglobin, eGFR, and serum creatinine, were extracted using electronic records. eGFR was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation.[122]

Participants self-reported their level of functionality using the basic Activities of Daily Living (ADL)[148] and Instrumental Activities of Daily Living (IADL) scale.[149] The ADL assesses the ability to perform six basic self-care tasks independently, with scores ranging between 0 and 6 for low to high level of functioning. The IADL assesses functionality to deal with more complex tasks, including handling of finance and managing medications. This tool contains eight items ranging from 0 for highly dependent individuals to 8 for those who are increasingly independent. Treating physicians also rated the functionality of the participants using the Karnofsky Performance Scale.[150] Scores range between 0 and 100, with higher scores corresponding to greater performance. Participants self-reported their desire for autonomy using the Autonomy Preference Indexes. This tool includes an eight-item decision-making scale (preference to be involved in decision-making) and a six-item information-seeking scale (desire to be informed) scales. Each of these scales were then standardised into scores ranging between 0 and 100.[151] Zero indicates low preference for autonomy (i.e. delegating to healthcare professionals), with 100 indicating a high preference and 50, a neutral attitude.[151,152] Cognitive functioning was objectively measured using the Montreal Cognitive Assessment (MOCA), with those scoring 26 or above deemed to have good cognitive functioning.[153] The Patient

Health Questionnaire, a 9-item diagnostic and assessment tool, was used to assess the presence and severity of depression.[154]

HRQOL was self-reported by participants at baseline and at follow-up using the Kidney Disease Quality of Life Short-Form health survey (KDQOL-36).[155] This tool consists of a combination of kidney disease-targeted items and generic items. The disease-specific part consists of eleven domains including two dialysis related domains. Therefore, nine domains assessing symptoms, effects, burden, work status, cognitive function, social interaction, sexual function, sleep, social support were applicable to this cohort. Participants responses were transformed into a 100-point scale, with higher scores reflecting better health. The short form (SF-36) is a 36-item questionnaire that assesses eight generic health domains, including comprising physical functioning, physical role limitations, pain, general health, vitality, social functioning and mental health. These domains are then aggregated into two component summary scores; physical health (PCS) and mental health component summaries (MCS), with higher scores reflecting greater self-reported HRQOL. Change in HRQOL was examined using the difference between baseline and follow-up MCS and PCS scores, with score differences of ≥ 5 considered clinically significant.[132]

Statistical analyses

Variables were checked for normality of distribution via visual inspection of histograms. Normally distributed continuous variables were reported as mean ± standard deviation (SD), and non-normally distributed variables were reported as median (interquartile range [IQR]). Frequency (percentage) was used to report proportions and categorical variables.

Participants characteristics were compared with respect to medication adherence (yes/no). Student's t-test was used to compare continuous variables with a normal distribution, while Mann Whitney-U test was applied for non-normally distributed variables. Chi-square test was used for comparison of categorical variables. Factors associated with medication non-adherence were examined using binary logistic regression, with effect sizes reported using odds ratios (ORs) and 95% confidence intervals (CIs). Factors were included in the final model based on a *p*-value <0.1 on univariate analyses or set *a priori* based on clinical importance and previous research.[25,132,134] The decision-making and information-seeking scales were treated in these analyses both as continuous and categorical variables. A cut-off point of 50 was used for categorising decision-making and information-seeking scales, as this score is considered to show neutrality in terms of increased preference for participation in one's care or delegating it

to healthcare professionals.[151] To identify factors associated with actual (MRCI) and perceived (PBM) medication burden, linear regression models were utilised, with associations reported using coefficients (β) and 95% CIs.

Finally, changes in different disease-targeted and generic HQROL measures at baseline and follow-up were compared using a paired t-test. Associations between medication non-adherence (MGLS) and changes in disease-targeted and generic HRQOL measures were performed using linear regression models, with analysis adjusted for age, gender, and baseline eGFR. Clinically significant changes in physical (PCS) and mental (MCS) quality of life measures was compared by adherence status using a Chi-square test. The median (IQR) changes in PCS and MCS over the follow-up period are illustrated using boxplots. A p <0.05 was set to determine statistical significance. STATA version 15.1 software (StataCorp LLC, TX) was used for analysis.

Results

Four hundred and sixty-four eligible individuals were invited to participate in the study (Figure 6.1.). Of these, 132 (28%) attended a baseline study clinic appointment and 101 (21%) participated in an additional medication interview. Subsequently, 63 (62%) of these participants have completed the follow-up interview. Participants at baseline were predominantly men (67%), with a mean age of 72 (SD 11) years and a mean eGFR of 21 (SD 6) mL/min/1.73m^2. Participants were not different from non-participants in terms of age and Index of Socioeconomic Disadvantage (p > 0.05). However, a higher proportion of non-participants were women (52% vs 32%, respectively; p = 0.04).

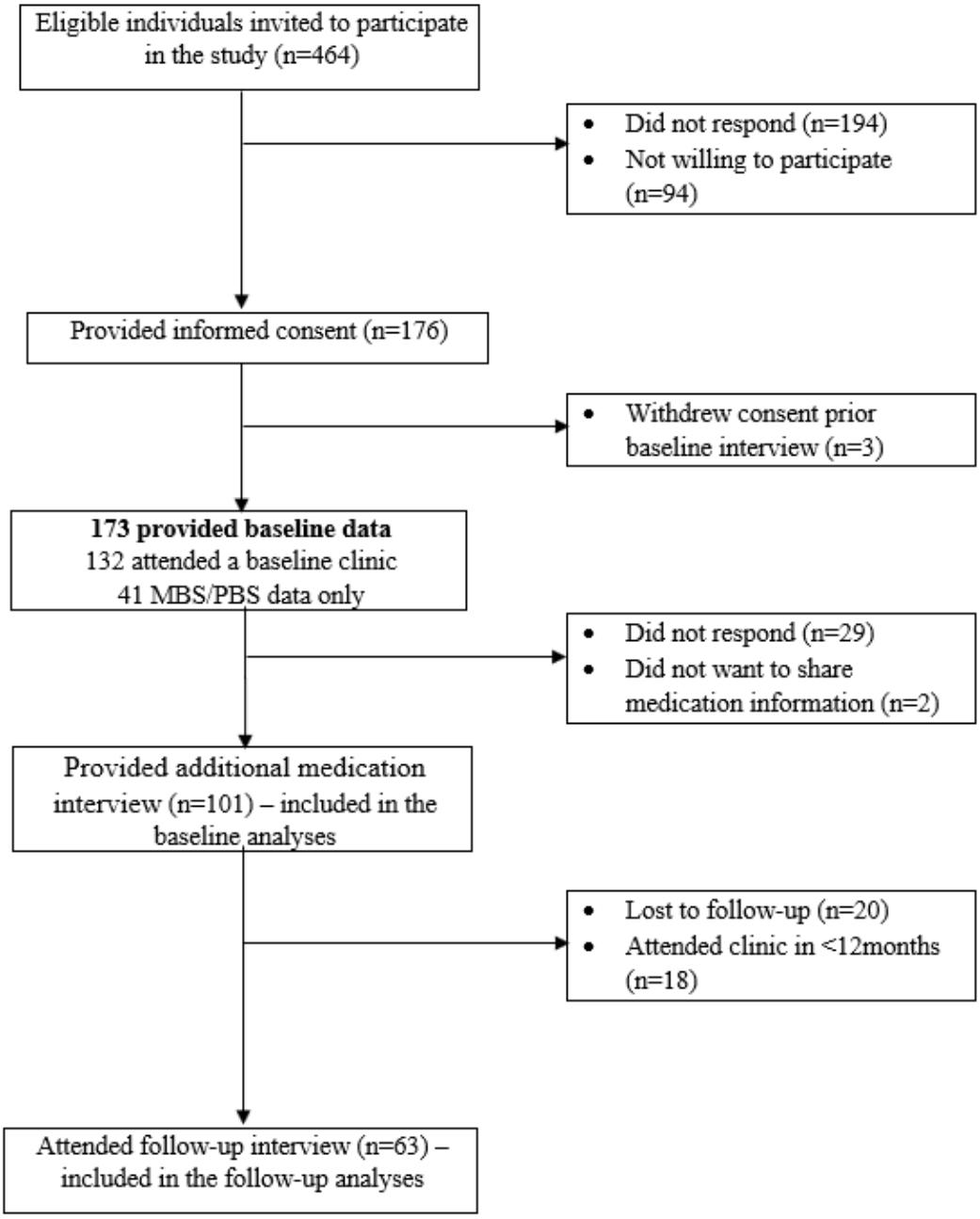

Figure 6.1. Flow diagram of the recruitment process

At baseline, 79% (80/101) of the participants were taking ≥ 5 medications and 43% (43/101) were taking ≥ 9 medications. Based on the MGLS, about 43% (43/101) of the participants were considered non-adherent, while 60% (61/100) reported suboptimal adherence based on TABS. API scores revealed that while most participants were interested in having more information (mean API information-seeking; 82 ± 11), they preferred healthcare professionals to make decisions for them (mean API decision-making; 45 ± 17). The baseline characteristics of participants by medication adherence are described in Table 3.

Table 3. Characteristics of participants by medication adherence (n=101)

		Adherence (MGLS)			Adherence (TABS)		
Variables	Total (n=101)	Yes (n=58)	No (n=43)	P	Yes (n=40)	No (n=61)	P
Sociodemographic							
Age (years)	72 (11)	73 (11)	70 (11)	0.12	74 (11)	70 (11)	0.06
Male gender, n (%)	68 (67)	36 (53)	32 (47)	0.19	31 (46)	37 (54)	0.08
Level of education (year 12 or less), n (%)	63 (62)	38 (60)	25 (40)	0.45	26 (41)	37 (59)	0.66
Married/de facto, n (%)	65 (49)	36 (55)	29 (45)	0.58	27 (41)	38 (59)	0.59
Government pension, n (%)	64 (63)	37 (58)	27 (42)	0.60	27 (42)	37 (58)	0.67
Index of Disadvantage (highest quartile)	33 (33)	19 (58)	14 (42)	0.30	11 (33)	22 (67)	0.47
Autonomy preference index							
Decision-making	45 (17)	42 (15)	49 (18)	0.04	41 (13)	47 (18)	0.10
Information-seeking	82 (11)	83 (11)	82 (11)	0.78	82 (11)	83 (11)	0.74
Karnofsky performance scale	87 (10)	86 (8)	88 (12)	0.54	87 (9)	86 (12)	0.65
Major depression (PHQ-9 score ≥ 10)	12 (12)	5 (42)	7 (58)	0.24	6 (50)	6 (50)	0.61
Clinical							
Smoking (former/current), n (%)	51 (50)	29 (57)	22 (43)	0.91	23 (45)	28 (55)	0.25
Comorbidity index, median (IQR)	3 (1-4)	3 (1-5)	2 (1-3)	0.38	3 (2-4)	2 (1-3)	0.04
Common comorbidities, n (%)							
Hypertension	90 (94)	52 (58)	38 (42)	0.71	38 (42)	52 (58)	0.67
Diabetes mellitus	39 (40)	28 (72)	11 (28)	0.02	13 (33)	26 (67)	0.19
Atherosclerotic disease	36 (37)	20 (56)	16 (44)	0.74	18 (50)	18 (50)	0.18
Congestive heart failure	17 (18)	7 (41)	10 (59)	0.12	9 (53)	8 (47)	0.27
Peripheral vascular disease	13 (13)	6 (46)	7 (54)	0.37	8 (61.5)	5 (38.5)	0.11
Malignant neoplasm	20 (21)	14 (70)	6 (30)	0.22	13 (65)	7 (35)	0.01
Body mass index, kg/m^2	30 (6)	31 (6)	30 (5)	0.67	28 (26-31)	32 (27-35)	0.02
ADL	5.8 (0.4)	5.9 (0.3)	5.7 (0.5)	0.10	5.8 (0.4)	5.8 (0.4)	0.36
IADL	5.5 (1.4)	5.5 (1.4)	5.2 (1.1)	0.06	5.4 (1.4)	5.6 (1.5)	0.34
Cognitive impairment (MOCA<26), n (%)	65 (67)	41 (72)	24 (60)	0.22	23 (35)	42 (65)	0.17
Laboratory							

Haemoglobin (g/L)	119 (18)	117 (15)	121 (22)	0.30	119 (20)	119 (17)	0.99
Serum creatinine (μmol/L)	265 (112)	249 (101)	288 (122)	0.03	266 (101)	265 (119)	0.97
eGFR (mL/min/1.73m^2)	21 (7)	22 (6)	21 (7)	0.51	21 (7)	21 (6.5)	0.89
Medical							
No. of medications, median (IQR)	8 (6-11)	8 (6-11)	8 (6-11)	0.73	8 (5-11)	8 (6-10)	0.73
MRCI, median (IQR)	19 (14-27)	20 (9-28)	17 (14-27)	0.41	19 (17-27)	19 (14-27)	0.76
PBM, median (IQR)	1.17 (1-1.33)	1 (1-1.33)	1.33 (1-1.33)	0.01	1 (1-1.33)	1.33 (1-1.33)	0.04
HRQOL (SF-36)							
PCS	39 (10)	39 (10)	39 (10)	0.65	39 (10)	39 (10)	0.96
MCS	51 (10)	51 (9)	50 (11)	0.62	51 (10)	51 (10)	0.96

Abbreviations: ADL, activities of daily living; BMI, body mass index; CCI, Charlson's comorbidity index; eGFR, estimated glomerular filtration rate; IADL, instrumental activities of daily living; IQR, interquartile range; MCS, mental component summary; MGLS, Morisky Green Levine Scale; MOCA, Montreal cognitive assessment; PBM, perceived burden of medication; PCS, physical component summary; PHQ-9, 9-item patient health questionnaire; SD, standard deviation; TABS, Tool for Adherence Behaviour Screening.
Results are presented in mean (SD) unless described otherwise.

Factors associated with medication non-adherence

Table 4a shows the effect of medication burden and other factors significantly associated with medication non-adherence (measured using the MGLS). People who reported non-adherence were more likely to report higher perceived medication burden (PBM) (OR 4.89; 95% CI 1.02-23.5; p=0.02) after adjusting for age, gender, eGFR, comorbidity and IADL. Actual medication burden (the number of medications and MRCI) were not associated with non-adherence. People with high desire for decision-making were 4.6 times more likely to report non-adherence compared with those who prefer to delegate decisions to healthcare professionals (adjusted OR 4.56 95% CI 1.68-12.35). Participants with diabetes were more likely to self-report being adherent (adjusted OR 0.36; 95% CI 0.14-0.89).

We also examined factors associated with suboptimal medication adherence assessed by the TABS (Table 4b). Both actual and perceived medication burden were not related to TABS adherence measurement. However, participants with high BMI (≥30 kg/m^2) were more likely to be non-adherent compared with those with normal BMI after adjusting for age, gender, CCI and eGFR (OR 3.81; 95% CI 1.01-14.5).

Table 4. Correlates of medication non-adherence

a. Non-adherence (MGLS)	Unadjusted ORs (95% CIs)	Adjusted ORs (95% CIs)*
No. of medications	0.97 (0.87-1.08)	0.96 (0.85-1.07)
MRCI (cont.)	0.83 (0.55-1.26)	0.89 (0.56-1.44)
PBM (cont.)	**4.02 (1.03-16)**	**4.89 (1.02-23.5)**
Having diabetes	**0.37 (0.15-0.91)**	**0.36 (0.14-0.89)**
Decision making (cont.)	**1.11 (1.001-1.23)**	**1.15 (1.02-1.29)**
Decision-making (cat; score >50)	**3.29 (1.41-7.69)**	**4.56 (1.68-12.35)**
b. Non-adherence (TABS)	Unadjusted ORs (95% CIs)	Adjusted ORs (95% CIs)
No. of medications	1.02 (0.91-1.13)	1.04 (0.92-1.18)
MRCI (cont.)	1.003 (0.96-1.05)	1.01 (0.96-1.06)
PBM (cont.)	3.67 (0.84-16.1)	2.78 (0.53-14.5)
BMI (≥30 kg/m^2)	2.85 (0.21-2.6)	**3.81 (1.01-14.5)**

API, Autonomy preference index; Cat., categorical; CIs, confidence intervals; Cont., continuous; MGLS, Morisky Green Levine Scale; PBM, Perceived burden of medications; ORs, odds ratios.
*Analysis adjusted for age, gender, eGFR, Charlson's comorbidity index and IADL.

Factors associated with perceived and actual medication burden

Given the strong association between perceived medication burden and medication non-adherence, we further explored factors associated with PBM (Table 5a). Higher number of medications (β 0.02; 95% CI 0.01 to 0.04) and MRCI scores (β 0.10; 95% CI 0.03 to 0.15) predicted higher perceived medication burden. Additionally, more frequent dosing intervals were also associated with higher perceived burden on adjusted analysis (β 0.02; 95% CI 0.01 to 0.03). After adjustment for gender, eGFR, CCI and IADL, advanced age was associated with lower perceived burden from medications (β -0.01; 95% CI -0.014 to -0.004). An increased desire for decision-making (β 0.02; 95% CI 0.01 to 0.03) and a higher desire for information (β 0.02; 95% CI 0.01 to 0.04) were also associated with higher perceived burden.

To examine if factors associated with perceived medication burden were different from those affecting actual medication burden (measured via MRCI), we investigated the correlates of MRCI (Table 5b). As expected, patients with diabetes had more complex medication regimens (β 7.54; 95% CI 3.43 to 11.6). Lower physical (SF36-PCS) (β -0.43; 95% CI -0.62 to -0.26) and mental HRQOL (SF36-MCS) (β -0.21; 95% CI -0.43 to -0.01) at baseline were associated with higher actual medication burden (MRCI). Participants with lower scores on kidney disease-targeted HRQOL measures, such as symptoms, effects and burden of kidney disease, and work status, had a higher actual medication burden. Of note, lower scores on these disease-targeted components indicate poorer health status in relation to the kidney disease. Table 5b

Table 5. Correlates of perceived and actual medication burden

a. **Perceived medication burden (PBM) – continuous**		
Variables	Unadjusted β (95% CIs)	Adjusted β (95% CIs)
No. of medications	**0.02 (0.01, 0.04)**	**0.02 (0.01, 0.04)**
MRCI (cont.)	**0.08 (0.02, 0.14)**	**0.10 (0.03, 0.15)**
Dosage form	0.023 (-0.001, 0.05)	0.024 (-0.001, 0.05)
Dosing frequency	**0.02 (0.01, 0.03)**	**0.02 (0.01, 0.03)**
Additional instructions	0.01 (-0.01, 0.02)	0.01 (-0.01, 0.03)
Age (cont.)	**-0.01 (-0.014, -0.004)**	**-0.01 (-0.015, -0.005)**
API Decision-making (cont.)	**0.02 (0.01, 0.03)**	**0.02 (0.01, 0.03)**
API Information-seeking (cont.)	**0.02 (0.01, 0.04)**	**0.02 (0.01, 0.04)**
b. **Actual medication burden (MRCI) – continuous**		
Variables	Unadjusted β (95% CIs)	Adjusted β (95% CIs)
No. of medications	**2.44 (2.26, 2.63)**	**2.49 (2.31, 2.67)**
Having diabetes	**7.31 (3.57, 11.1)**	**7.54 (3.43, 11.6)**
Kidney disease-targeted scales		
Symptom	**-0.26 (-0.38, -0.15)**	**-0.25 (-0.37, -0.17)**
Effects of kidney disease	**-0.19 (-0.34, -0.06)**	**-0.23 (-0.39, -0.08)**
Burden of kidney disease	**-0.12 (-0.19, -0.04)**	**-1.64 (-0.25, -0.08)**
Work status	**-0.09 (-0.15, -0.04)**	**-0.09 (-0.14, -0.03)**
SF-36 generic scales		
MCS	-0.15 (-0.35, 0.04)	**-0.21 (-0.43, -0.01)**
PCS	**-0.43 (-0.61, -0.26)**	**-0.44 (-0.62, -0.26)**

API, autonomy preference index; Cont., continuous; MRCI, medication regimen complexity index; MCS, mental component summary; PCS, physical component summary; SF-36, 36-item short form survey.
Analysis adjusted for age, gender, Charlson's comorbidity index, activities of daily living (IADL) and cognitive functioning (MOCA).

Changes in HRQOL and its association with medication non-adherence (MGLS)

The mean ± SD follow-up time for participants who completed the second interview was 433 ± 82 days (~14 months), with no difference in follow-up duration observed between adherent vs non-adherent groups (436 ± 88 vs 430 ± 77 days; p=0.76)

The changes in different components of HRQOL, both kidney disease-targeted and generic SF-36 scales, are presented in the Appendix D attached. Follow-up data were completed by 63 and

60 participants for kidney-disease targeted scales and generic SF-36 scales, respectively. Out of the disease-targeted components, only the burden of kidney disease has shown a significant change at follow-up (mean ± SD score declined from 77 ± 25 to 70 ± 31; p=0.01). Overall, there was no association between medication adherence and changes in kidney disease-targeted scales over time.

Of 60 participants with completed generic HRQOL data (SF-36), a decline of any magnitude in physical and mental HRQOL was observed in 58% of them at around 14 months of follow-up. A clinically significant decline in physical HRQOL(change in SF36-PCS≤5) was observed in 35% of participants overall, representing 26% of adherent and 45% of non-adherent participants (p=0.20). A significant reduction in mental HRQOL was also observed in 35% of participants overall, which represented 42% of adherent and 28% of non-adherent individuals (p=0.16).

As illustrated in Figure 6.2., the physical HRQOL was improved over time in adherent individuals compared with a decline in their non-adherent counterparts (a median [IQR] change in PCS of 1.5 [-5.3 to 7.6] vs -3.4 [-9.1 to 0.9]; p=0.06). Further, medication non-adherence has shown a significant negative association with a change in physical HRQOL after adjusting for age, gender, and baseline eGFR (β -4.64; 95% CI -9.10 to –0.17). There was no association between medication non-adherence and a change in mental HRQOL before or after adjustment for the same variables. Table 6

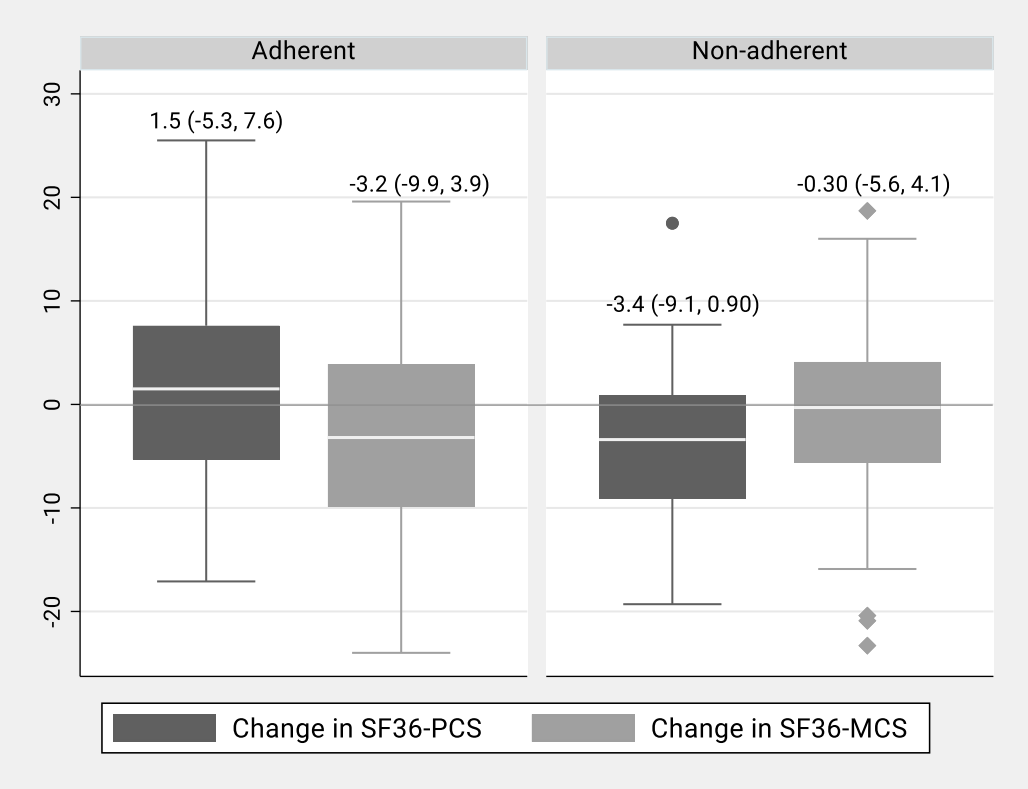

Figure 6.2. Changes in physical (SF36-PCS) and mental (SF36-MCS) health-related quality of life over 14-months by adherence status (MGLS).

Table 6. The association between medication non-adherence (MGLS) and changes in physical and mental health-related quality of life health over time

	Unadjusted β (95% CIs)	Adjusted β (95% CIs)*
SF36-PCS		
Non-adherence	-3.99 (-8.29, 0.31)	**-4.64 (-9.10, -0.17)**
SF36-MCS		
Non-adherence	1.82 (-3.12, 6.78)	2.03 (-2.99, 7.05)

*analyses adjusted for age, gender and baseline eGFR

Abbreviations: CIs, confidence intervals; MGLS, Morisky Green Levine Scale; SF36-PCS, short form physical component summary; SF36-MCS, short form mental component summary; physical component summary.

Discussion

This study indicates that a considerable proportion of adults with pre-dialysis CKD are non-adherent to their medications. The 43% medication non-adherence (MGLS) was lower than that reported by an Australian study on dialysis patients that used the same questionnaire, where 57% of participants were non-adherent.[140] This is understandable given the relatively higher medical complexity in dialysis patients than at earlier stages of CKD.[140,156] Of note, a greater proportion of suboptimal adherence (60%) was identified via the TABS questionnaire. This could relate to the differences in the constructs of the two questionionnaires.[18,143] In addition to medication adherence, the TABS, for example, also captures patients' experiences and behaviour concerning disease management.[144] This shows that medication non-adherence is multidimensional in nature and needs different strategies to detect in patients with pre-dialysis CKD.

Importantly, perceived burden (PBM) of medications, not the actual burden, was associated with medication non-adherence. The association between PBM and non-adherence is in contrast with a prior Australian study that showed no relationship between these factors.[140] A study from Italy showed that perceived burden can modulate the relationship between medication regimen complexity and adherence in dialysis patients.[25] In this study, Neri et al found that each pill that was added to a regimen of a patient with low PBM was associated with a 5% increase in the odds of non-adherence.[25] This was not the case in those with high PBM, where regimen complexity was not associated with non-adherence.[25] The findings highlight the need to evaluate the perceived burden, alongside actual medication burden, to optimise adherence. Also, simplifying a medication regimen may not effectively improve adherence unless patients' perceptions are concomitantly addressed.[25]

Another interesting result from this study was that people with an increased desire for autonomous decision-making were more likely to be non-adherent. This corresponds with a finding from a study on patients with asthma that applied the same set of questionnaires.[157] The relationship between desire for decision-making and non-adherence could relate to intentional non-adherence, where patients make a conscious decision to skip medications. This phenomenon has been explained by a qualitative review that identified 'rationalised non-adherence' as a mechanism used by patients to avoid treatment disruptions of their daily routine.[158] A similar finding was reported in dialysis recipients where people tended to consciously overlook treatments, which the authors termed 'active non-adherence.'[159] This is

particularly common with medications they considered less important or less easy to adhere to.[159] Therefore, there is a need to foster optimal patient-centred care to actively engage patients in conversations that enable them to acknowledge medication-related difficulties in view of improving adherence.[158] Reiterating the importance of medications in slowing disease progression at point of care could also help improve adherence. Finally, obese participants (BMI $\geq$30kg/m^2) were more likely to be non-adherent than people with normal BMI based on the TABS. The relationship between higher BMI and poor adherence has been reported in older men previously.[160] This association could be because non-adherence in these individuals might also extend to exercise or dietary restrictions.[160]

Highly complex regimens and more frequent dosing were associated with higher perceived medication burden, while older age was associated with feeling lower burden. The association of regimen complexity and more frequent dosing with perceived treatment burden has been reported.[161,162] These factors are important given their practical relevance and relative ease to be targeted by interventions seeking to reduce medication burden.[161] For instance, the use of long-acting alternatives instead of repeated use of immediate-release medications is one strategy that can be used to reduce the dosing frequency. Nevertheless, it is important to understand that even less complex regimens could prove burdensome in some patients.[162] Particularly, patients with limited cognitive functionality or with little support could be affected in this regard. The association between older age and lower perceived treatment burden is in line with prior studies.[25,161,162] This may be associated with older people's adaptation to medications after long-term use.[161] Older adults may also consider their medications more a matter of necessity rather than a burden.[161]

Lower HRQOL (kidney disease-targeted and generic scales) were predictive of actual medication burden (MRCI). The association between HRQOL measures and regimen complexity was independent of Charlson's comorbidity score, suggesting that regimen complexity may capture additional information on the overall disease status of patients.[156] This may also strengthen our prior hypothesis than regimen complexity could serve as a proxy measure of overall health in patients with CKD.[163] Also, an inverse relationship between medication burden and HRQOL has been previously reported in pre-dialysis patients with CKD.[141]

Medication non-adherence was not associated with baseline HRQOL; however, it was associated with a significant decline in physical, but not mental, HRQOL (SF36-PCS) even

over a short follow-up time. This finding was despite the significant decline in mental HRQOL during follow-up for all participants. A study from the AusDiab cohort previously reported that a physical decline in HRQOL is dependent on baseline eGFR values.[132] However, we found no statistically significant association between baseline eGFR and changes in HRQOL over time.

This study has some strengths and weaknesses. Examining people with advanced CKD not receiving renal replacement therapy adds a new perspective to the literature, as patient-reported medication experiences in this patient group are currently lacking. This is also the first study to examine the association between medication non-adherence and a change in HRQOL over time in patients with CKD. The inclusion of in-depth patient, clinical, medication and social factors is another strength of this study. The relatively small number of participants included may limit the generalisability of the study; however, recruiting people with relatively poorer health and lower functional status is difficult.[142] The use of self-report, but not objective measures, to assess adherence is another limitation of the study, as non-adherent behaviour is often under-reported due to social desirability bias. However, self-reported adherence measures have an advantage in terms of ease of implementation in real practice. In addition, the self-report measures applied in this study capture both intentional and unintentional adherence.

Conclusion

This study indicates that medication non-adherence is common in adults with pre-dialysis CKD. Perceived medication burden was a predictor of non-adherence, highlighting the need to incorporate patient-reported medication experiences in routine CKD care. Further, while medication regimen complexity was negatively associated with both physical and mental HRQOL at baseline, non-adherence was associated with a decline in physical HRQOL over time. This finding suggests the potential role of medication-related factors in modifying patient-centred outcomes and the need for further research to better understand this relationship.

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Summary

The study above shows that medication adherence and burden are important medication-related factors that are associated with patient-centred outcomes. In the next chapter the role of pharmacist medication review on medication appropriateness in CKD patients is explored.

7. CHAPTER SEVEN: Effect of pharmacist-led medication review on medication appropriateness in older adults with chronic kidney disease

Overview

This chapter presents a study addressing the fifth objective of the thesis. In this work, the effect of medication review conducted by pharmacists on medication appropriateness in older patients with CKD is explored targeting a tertiary care public hospital in Tasmania.

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Summary

This chapter examined the role of routine medication review by clinical pharmacists on medication appropriateness in older adults with CKD. The results show that collaborative efforts by clinical pharmacists and physicians can lead to a significant improvement of medication appropriateness in older adults with CKD. The lack of medication review in more than half of the patients included also revealed the need to upscale the role of pharmacists.

The next chapter presents the general discussion of all studies in this PhD thesis, including practical implications and future directions.

8. CHAPTER EIGHT: General discussion and conclusion

This thesis presents multiple interconnected studies that examine medication-related factors and outcomes in patients with CKD, considering prescriber, medication regimen, the healthcare environment, and patient factors. A combination of methods, including retrospective and prospective cohorts and a systematic review, were applied to address the specific objectives of the thesis. As a starting point, a systematic review of the literature was conducted to summarise the evidence on inappropriateness of medication use in patients with CKD across different healthcare settings. Based on the gaps identified in the review, consecutive studies were performed to investigate medication inappropriateness and associated outcomes in patients with CKD. Following on from this, the relationship between medication-related factors and outcomes, such as hospital readmission and HRQOL, was examined. The effect of the healthcare environment and, the care involved, in modifying medication appropriateness was assessed focusing on a public hospital setting. The author also expanded on evaluating the role of pharmacist-led medication review in improving the quality use of medicines in older hospitalised patients with CKD.

The following vignette, which is based on a patient from the research included in this thesis, illustrates how medication-related factors in a patient with CKD could contribute to, and be influenced by, hospitalisation.

A 66-year-old adult with stage 3 CKD (eGFR 42 mL/min/1.73m^2) living at home was admitted to a tertiary care hospital due to shortness of breath because of pre-existing congestive heart failure (left ventricular ejection fraction=35%). Comorbidities at admission included congestive heart failure, diabetes mellitus (type 2), ischaemic heart disease, dyslipidaemia and hypertension. Findings suggested poorly controlled hypertension (blood pressure=173/99 mmHg), diabetes (HbA1c=9.6%), and dyslipidaemia (total cholesterol=9.8mmol and LDL=7.5mmol) that probably contributed to hospital readmission. On hospital admission, the patient was prescribed seven different medications, including oral and parenteral dosage forms, and medications with multiple dosing intervals (MRCI=19). The number of medications increased to nine at discharge after efforts to manage the patient's conditions (MRCI=23.5). It was during a routine inpatient medication review that a pharmacist was able to detect long-standing medication non-adherence, and this was verified using community pharmacy records (patient did not refill prescriptions from pharmacy for almost three months). Therefore, poor

adherence to the prescribed medications prior to admission resulted in suboptimal medication use, and likely contributed to hospitalisation.

The detection of medication non-adherence by a pharmacist shows an opportunistic identification of a medication-related problem during hospitalisation. As noted, poor adherence to multiple medications, including those for congestive heart failure, was highly likely to have caused the hospitalisation in the abovementioned vignette. The findings also indicated long-standing poor adherence to antihypertensive and antidiabetic medications. The need to prescribe additional medications during hospitalisation to manage the patient's conditions resulted in a more complex regimen at discharge than admission, indicating how one medication problem can potentially lead to another.

This thesis was designed with the notion that problems like the one illustrated in the vignette are common in patients with CKD and could be identified and prevented or corrected at different stages of patient care.

8.1. Systematic Review

The systematic review (described in Chapter 2) revealed that inappropriate medication use in patients with CKD is common and highly variable across different countries and healthcare settings.[17] It was observed from the systematic review that a range of renal dosing guidelines has been employed to define medication inappropriateness in CKD, which may have contributed to the wide variation in the prevalence of inappropriate prescribing. Some of the discrepancies among the different renal dosing guidelines have been demonstrated in a previous study.[164] Another probable cause for the observed differences in inappropriate prescribing is the varied use of renal function measures and dosing equations (CG, MDRD or CKD-EPI). Regardless of these variations, the results of the review indicated that medication inappropriateness is common in patients with CKD and there is a need for cautious use of renally-cleared medications in these patients.

The systematic review also revealed that interventions in the form of pharmacist involvement and computerised decision support systems were effective in reducing the prescribing of renally-cleared and nephrotoxic medications in patients with CKD. Substantial improvement was particularly observed when physicians receive immediate feedback from pharmacists, showing the relevance of the input from clinical pharmacists in CKD care. Other reviews that

investigated the impact of clinical pharmacy services in the management of CKD also showed promising outcomes, although there was a lack of high-quality data in this area.[165,166]

The systematic review identified some gaps in the literature that need further research attention. One of the main gaps was the limited number of studies that reported clinical outcomes attributed to the use of inappropriate medications. Further, most of the studies simply reported prevalence of inappropriate medication use, with a small number of studies performing regression analyses to identify predictors of medication inappropriateness. Finally, it was observed from the systematic review that research including patients with CKD was highly focussed on examining the extent of dosage adjustment of renally-cleared medications or avoidance of nephrotoxic medications.[17] However, patients with CKD, especially those older than 65 years, are expected to have a higher risk of medication inappropriateness due to the age- and CKD-related functional decline. Therefore, the author hypothesised that older adults with CKD would be predisposed to additional inappropriate medications than those that can be determined solely based on renal function.

8.2. Main research findings

The different studies included in this thesis showed that adults with CKD are prone to high level of medication inappropriateness, regimen complexity and medication non-adherence. The results also indicated that medication-related factors in patients with CKD could relate to clinical and patient-reported outcomes and be influenced by the healthcare service provided, including hospitalisation and pharmacist-led medication review.

8.2.1. Medication inappropriateness, its predictors and medications involved

In Chapter 3, medication inappropriateness was assessed in older patients with CKD using tools that are applicable in older adults, the MAI and Beers criteria. The findings revealed that applying such tools can identify added risks in older patients with CKD. This corroborates the hypothesis that these patients have a higher risk of medication inappropriateness.[167] Issues related to medication dosing and medication-medication and medication-disease interactions were particularly frequent in older patients with CKD. This result shows the importance of integrating the use of established criteria to holistically capture MRPs in this patient group.

The research also explored factors associated with medication inappropriateness in older patients with CKD. The number of medications and eGFR were identified as the main predictors of medication inappropriateness.[167] This result is consistent with the findings from

the systematic review, where polypharmacy and lower eGFR values were associated with PIMs use.[17] The use of multiple medications is not only responsible for PIMs, but increases the probability of adverse drug reactions occurring,[168] emphasising the need to be vigilant in patients with many medications. The association between lower eGFR and medication inappropriateness is likely in part due to the need for several dosage adjustments at advanced stages of CKD. Identifying these factors as predictors of medication inappropriateness is important given their accessibility in both community and institutional settings.

The thesis' findings revealed that various classes of medications were inappropriately prescribed in older patients with CKD (shown in Chapter 3).[167] Cardiovascular agents were the most commonly, and inappropriately, prescribed medication according to the different criteria the author employed.[167] The reason for this could relate to the substantial cardiovascular disease burden in patients with CKD.[114] It is important to note that cardiovascular conditions were also the most common comorbidities involved with hospitalisation and hospital readmission (Chapter 4 and 5). Therefore, improved identification of inappropriateness of cardiovascular medications has potential health ramifications in patients with CKD. Also, giving extra attention to patients with CKD and coexisting cardiovascular conditions would be beneficial to most adults with CKD.

PPIs were another class of medications that were often prescribed potentially inappropriately with no indication or for a longer duration than recommended.[45] These medications are associated with a range of possible adverse effects, including increased risk of infection, bone fracture, and deficiencies of vitamins and minerals.[169] The most important potential adverse effects in patients with CKD, however, are renal incidents, including disease progression and AKI.[170-172] This indicates the need for heightened attention by healthcare professionals to assess the appropriateness of indications and duration of therapy with PPIs in patients with CKD. It should also be noted that, given the mounting evidence of over-prescribing of PPIs, there are now restrictions in place through the PBS to reduce the use of these medications in the Australian context (1st May 2019).[173]

The inappropriate prescribing of benzodiazepine receptor agonists and psychotropics with strong anticholinergic properties in older patients with CKD was another problem identified.[167] Importantly, these medications were prescribed in the context of dementia, cognitive impairment, history of falls and delirium, further increasing the risk of adverse effects. This finding should be seen in the light of recent evidence in patients with CKD that reported the

association between psychotropic drug use and adverse outcomes, such as altered mental status, falls and fractures.[174] The author also found out that 1 in 10 readmissions within 30 days was related to falls and associated fractures (Chapter 5).[175] Therefore, ensuring the judicious use of these medications is imperative to minimise medication-related harms, including falls and unplanned hospital readmission. This could include a thorough assessment of the risks and benefits of these medications and consideration of their deprescribing when the individual risks outweigh the benefits.[176]

8.2.2. Medication-related factors and hospital readmission

In Chapter 4 and 5, the association between medication-related factors and hospital readmission was explored. The findings indicated that patients taking RAS blockers had lowered hospital readmission risks within 30 and 90 days, compared with those not on these medications (Chapter 4).[163] Yet, these medications were prescribed only to half of the patients included in our study, as shown in Chapter 4. Understandably, adverse effects to such medications, such as hyperkalaemia, AKI, and hypotension, could limit the use of these medications in highly sensitive older adults.[177] However, the findings suggest that these medications could be associated with a lower risk of readmission in these patients. This finding is also supported by guidelines, such as the KDIGO and Kidney Health Australia-Caring for Australasians with Renal Impairment (KHA-CARI), on using these medications in both diabetic and non-diabetic patients with CKD to reduce proteinuria and thus improve outcomes.[86,87]

Medication inappropriateness, although relatively higher in people with 30-day and 90-day hospital readmissions, was not an independent predictor of hospital readmission in older patients with CKD. However, as shown in Chapter 4, people with higher level of medication inappropriateness were likely to return to hospital relatively sooner than those with lower medication inappropriateness. This shows the potential importance of a thorough medication review using standard tools like Beers criteria and components of the MAI to identify patients who can benefit from interventions and post-discharge follow-up care.

The studies presented in this thesis also explored the relationship between medication regimen complexity and health outcomes (presented in Chapter 5). Medication regimen complexity was quantified using a validated tool that considers not only the medication count but also the dosage forms, dosing frequency and additional instructions.[18] Higher regimen complexity was associated with a shorter time to 12-month readmission after adjusting for covariates, including Charlson's comorbidity index. The association between regimen complexity (MRCI) and 12-

month time to readmission independent of Charlson's comorbidity index suggests that MRCI may capture burden of disease in patients with CKD over and above that measured by the comorbidity measure. Therefore, regimen complexity measured via the MRCI could serve as a proxy measure of overall health status in older patients with CKD, particularly in settings with limited available clinical information.

Medication regimen complexity (medication count or MRCI) may also be a source of perceived burden of medications. This has been explored in this thesis by examining the relationship between medication regimen complexity and self-reported perceived burden of medications, targeting pre-dialysis patients with CKD (Chapter 6). The results revealed a positive association between the two variables. Higher perceived medication burden, in turn, was associated with poor medication adherence in these patients. This highlights the importance of assessing patients' medication-related perceptions and experiences as part of routine medication reviews to better target individuals who can benefit from interventions seeking to improve adherence.

8.2.3. The effect of hospitalisation and pharmacist intervention

This thesis indicated that medication inappropriateness, despite its significant reduction after hospitalisation, was still substantial at hospital discharge (Chapter 3).[167] Hospitalisation brings an opportunity for healthcare professionals to re-evaluate and, thus, identify medications that no longer have benefits or identify new risk factors if the patient's condition has changed. However, the substantial medication inappropriateness based on the MAI and Beers criteria at hospital discharge indicates that older patients with CKD have an added risk that is potentially being missed despite this opportunity brought by hospitalisation. This shows the continual need to raise the awareness of clinicians, including pharmacists, about CKD, PIMs use and the different criteria available to identify them. Also, evidence-based educational sessions about the clinical consequences of PIMs may help reinforce the prescribing of appropriate medications in these patients.[62]

As a continuation of investigating the effect of hospitalisation, the impact of pharmacist-led medication review on medication inappropriateness was investigated in Chapter 7, targeting older patients with CKD. Overall, pharmacist-led medication review was conducted in less than half of patients targeted in this study, indicating the need to deliver a standardised clinical pharmacy service to all inpatients. The findings also revealed pharmacist-led medication review led to a significant reduction in medication inappropriateness, albeit this reduction was

not significantly better than that observed with hospitalisation alone. However, the trend was indicative of greater improvement with pharmacist medication review, especially upon implementation of pharmacists' recommendations by physicians.

Pharmacists were likely to recognise renal impairment, and thus suggest dosage adjustments of renally-cleared medications in older patients with CKD. This is important because one of the prescribing considerations in patients with CKD is minimising adverse events due to medications that need dosage adjustment in renal impairment. In contrast, assessments of medication adherence and medication interactions (with other medications, diseases or laboratory) were often overlooked by pharmacists during medication review. Therefore, expanding pharmacist's involvement in these aspects would be valuable to further improve quality use of medicines in patients with CKD. The Standard of Practice developed by the Society of Hospital Pharmacists Australia for renal pharmacists can be used by pharmacists involved in CKD care to provide enhanced and standardised services.[178]

8.2.4. Medication burden and patient-centred outcomes

In Chapter 6, the associations between medication burden and non-adherence, and HRQOL were examined targeting adults with pre-dialysis CKD. This study revealed that a significant proportion of adults with pre-dialysis kidney disease were non-adherent to their medications. Interestingly, it was the perceived burden of medications, not the actual burden, that predicted non-adherence behaviour in these participants. This result indicates the need to integrate the assessment of medication-related experiences and perceptions as part of routine medication review to improve medication adherence in these patients.

This study also examined the effect of medication regimen complexity and adherence on kidney disease-targeted and generic HRQOL measures. These measures capture both physical and mental health status, as self-reported by participants. The findings revealed that while medication regimen complexity was negatively associated with both physical and mental HRQOL at baseline, medication non-adherence was predictive of a decline in physical HRQOL over time. These results are important given the modifiable nature of medication-related factors, such as regimen complexity and non-adherence.

Patient-centred outcomes, such as HRQOL, are important outcome measures with implications for patients, healthcare providers, and payers.[132] This research is one of the few studies that examined patient-centred outcomes in pre-dialysis patients with CKD and therefore contributes

to an emerging unique evidence base in these patients. Understanding medication-related factors affecting patient-centred outcomes is instrumental to inform decisions in CKD treatment and strategies. The change in HRQOL, and how this is affected by medication-related factors, can offer some insight for earlier care planning in advanced CKD. For example, the main target of medication therapy in patients who receive supportive (conservative) CKD care instead of RRT is to improve the HRQOL. Therefore, planning feasible regimens and ensuring optimal medication adherence would play an invaluable role in symptom management and consequently improve HRQOL in these patients. Improving HRQOL has, in turn, broader clinical relevance in terms of long-term prognosis, as poorer HRQOL was linked with higher risk of hospitalisation and mortality in patients with CKD.[179]

8.3. Strengths and limitations of the studies

In this thesis, the author has attempted to fill the evidence gap regarding medication-related outcomes in patients with CKD using prospective and retrospective study designs. However, these studies had their own limitations. One of the limitation of the retrospective studies is the relatively small sample size employed (Chapter 3, 4, 5 & 7). This may partly explain the lack of statistically significant associations between medication-related variables (regimen complexity and appropriateness) and readmission within 30 and 90 days of discharge.

The prospective cohort, as shown in Chapter 6, also consisted of a relatively small number of participants. However, this cohort solely included people with advanced CKD on pre-dialysis stage who, therefore, had multiple comorbidities. Thus, the relatively small number of participants was anticipated based on previous report.[142] Nevertheless, the inclusion of a range of sociodemographic, psychosocial, medical, clinical and HRQOL information (with a follow-up data) was the main strength of the study.

In the medication appropriateness studies (Chapter 3, 4 and 7), the use of MAI, an implicit measure that requires clinical judgement, may have introduced some level of subjectivity. However, the assessment tool (MAI) is enriched with several explicit referential guides to be used during rating that somewhat minimises the subjectivity of evaluation. Another drawback with the use of this tool is the time it takes, which makes it less practical to implement in the real-world scenario. However, the author also used the Beers criteria (an explicit tool), alongside MAI, to identify medications that were potentially inappropriate in these patients, which can be considered as the strength of the research.

The author has used two different cohorts (retrospective and prospective) to investigate the effect of medication regimen complexity on medication non-adherence and hospital readmission. These cohorts targeted older hospitalised patients with CKD (retrospective) and adults with advanced pre-dialysis CKD living in the community (prospective). Therefore, targeting these vulnerable population groups in the studies can be considered as the strength of the overall research. However, the findings should be interpreted in the context of adults with eGFR <60mL/min/1.73m^2 and not on renal replacement therapy.

People with complex regimens, such as older patients with CKD, may not only be predisposed to errors of (prescribing) commission but also of omission. In this thesis the author primarily focused on the former. Despite the high number of medications used in these patients, it is possible that there may have been under-prescribing of beneficial medications. The author did not used structured tools, like START criteria,[47] to assess prescription omissions in these patients. However, the author examined the association between different classes of medications and hospital readmission in older patients with CKD. This analysis revealed that users of RAS blockers had improved outcomes compared with their non-user counterparts.[163]

The assessment of medication adherence was solely based on self-report by study participants. This method has its limitations as adherence is over-estimated when self-reported, largely attributed to social desirability bias.[22] However, having this limitation in mind, the author applied two self-report measures to ascertain the magnitude of medication non-adherence in CKD.

8.4. Research and practice implications, and future directions

The high level of medication inappropriateness identified using the MAI and Beers criteria indicates the importance of using standard criteria to assess medication appropriateness in CKD. Healthcare professionals, including pharmacists, should implement the different criteria developed for identification of medication inappropriateness. For example, explicit measures like the Beers criteria can be used in combination with clinical judgment to identify PIMs in clinical practice. The updated Beers criteria now include a list of medications that need to be adjusted in CKD and include clinically important medication interactions.[45] Also, the author found that the having higher number of Beers criteria medications was predictive of a higher level of medication inappropriateness measured via MAI.[167] Therefore, Beers criteria, alongside renal dosage guidelines, can be used to ensure the quality use of medicines in CKD patients. The Beers criteria can be a particularly useful tool to provide a more robust medication

review as part of Home Medicines Reviews in an Australian community setting. Beers criteria, as an explicit measure, are also relatively easy to integrate into clinical decision support systems within an electronic medical record in a hospital setting.

Although not statistically significant, findings in the thesis showed that people who were readmitted within 30 and 90 days of hospital discharge had a higher level of medication inappropriateness. The lack of statistical significance could be related to the relatively small sample size included in the study. Therefore, future work targeting larger samples of older patients with CKD should examine the relationship between these medication-related variables and hospital readmission.

The association between the use of RAS blockers and lower readmission risk is another important finding that merits further research. Future studies targeting larger populations are important to confirm the importance of the use of these, and other renoprotective medications, in modifying renal and cardiovascular morbidity in older adults with CKD. Of note, emerging evidence has demonstrated that sodium-glucose cotransporter 2 inhibitors could be potential (or better) alternatives in improving outcomes in diabetic patients with CKD.[180,181] Therefore, comparative studies between these medication classes in improving cardiovascular and renal outcomes have the potential to redefine clinical practice, particularly in diabetic patients with CKD.

The relationship between perceived medication burden and medication non-adherence is an area that needs further investigation. There is a need to assess medication-related perceptions and experiences using detailed and more structured questionnaires that capture different medication aspects, such as the Living with Medicines Questionnaire,[182] in patients with CKD. A qualitative investigation of treatment burden in patients with CKD, especially in those with multiple comorbidities, would also be important to better understand this problem and propose interventions to minimise it.

The thesis showed the potential of pharmacist-led medication review in improving medication appropriateness, especially when the recommendations were acted upon by physicians. The vignette shown above also demonstrated the practical relevance of pharmacists' interventions. This finding strengthens the evidence on the positive outcomes, including improved medication adherence, associated with pharmacist involvement in CKD patient care.[166] However, there is a lack of sufficient high-quality randomised trials on pharmacist interventions in patients with CKD, especially in those at the pre-ESKD stage.[166] Therefore, more research focusing on the

effect of pharmacists' involvement on different clinical, humanistic (for example, HRQOL) and economic outcomes is imperative in patients with CKD not receiving RRT.

Future studies should also investigate whether medication management interventions especially tailored according to therapeutic goals of patients with CKD would be more effective than a routine medication review in improving the quality use of medicines. Given the overwhelming evidence on the effect of pharmacist involvement is related to a hospital setting, it is important to investigate the role of pharmacists in community settings. This can be done, for example, by assessing the impact of Home Medicines Reviews in improving medication appropriateness and associated outcomes. It would also be important to investigate if medication review by pharmacists translates to improved clinical outcomes in patients with CKD.

Finally, despite the growing body of information about the involvement of pharmacists in the care of patients with CKD, the quality of most of the works remains relatively poor.[166] In addition to the lack of high-quality studies, the limited randomised controlled trials in patients with CKD (mainly in ESKD) also reported inconsistent outcomes regarding pharmacist-led interventions.[166] Therefore, there is a need for further high-quality randomised trials to evaluate the impact of pharmacists in CKD care. Further, well-designed observational studies can also shed light into the role of pharmacists in a real-world scenario and thus shape their involvement in nephrology practice.

9. CHAPTER NINE: Conclusions and recommendations

Collectively, the studies included in this thesis fill an evidence gap in relation to medication-related factors predicting health outcomes in patients with CKD. Also, it adds to the emerging unique body of evidence in relation to patient-centred outcomes in advanced pre-dialysis CKD. The findings indicated that potentially inappropriate medications use is common and can be better identified using robust criteria developed for use in older people. Improved identification of inappropriate medications can be achieved by creating a means to raise the awareness of healthcare professionals about the use of standard criteria in identifying problematic medication regimens.

The thesis revealed that the use of RAS blockers could be particularly beneficial to older adults with CKD, as shown by lowered risks of readmission within 30 and 90 days of hospital discharge. Therefore, it is imperative that clinicians consider the use of these medications in all older patients with CKD unless there is a clear contraindication precluding their use.

Medication regimen complexity is another important parameter with a potential impact on health outcomes in patients with CKD. This is shown by the shorter time to readmission of people with highly complex medication regimens within one year of hospital discharge. The use of medications with multiple frequencies of administration and different dosage forms is common in patients with CKD. Therefore, assessment of all these medication attributes, alongside medication count, can be important in identifying inappropriately complex regimens. This is crucial for targeting patients that can benefit from regimen simplification strategies.

The other important finding in this thesis is the high prevalence of medication non-adherence in advanced pre-dialysis patients with CKD, and how that could relate to a change in physical HRQOL over time. This work can be considered as an important starting point to further explore the longitudinal relationship between modifiable medication-related factors and patient-centred outcomes. Understanding patient-centred outcomes in pre-dialysis CKD is particularly important in informing decisions regarding treatment options and to implement quality improvement strategies. This finding is, therefore, an important step forward in this regard and reinforces the use of patient-reported outcomes as an integral part of CKD patient care.

The importance of the care received during hospitalisation, including medication review by pharmacists, in improving medication appropriateness is another key result of this thesis. The

opportunistic identification of medication non-adherence during hospitalisation (as shown in the vignette above) is illustrative of how the different points in the care continuum can be used to reassess medication-related issues in patients with CKD.

In summary, the author believes that this thesis contributes significantly to the medication-related outcome research in CKD. Based on the findings of this thesis, the author recommends for:

- Periodic re-evaluation of patients' medication regimens considering comorbidities and overall health condition using standard criteria aiming to improve the quality use of medicines, especially when the opportunity arises at different points of contact across the care continuum.
- Assessment of patient-reported medication experiences, in addition to the number of medications and regimen complexity, to fully capture barriers to medication adherence and propose strategies to improve adherence.
- Identification of 'inappropriately' complex medication regimens considering the dosage forms, dosing frequency or additional directions provided by physicians to target patients who can benefit from regimen simplification strategies.
- Consideration of the competing tensions between reducing regimen complexity and the use of all beneficial medications. The use of RAS blockers, for example, should be routinely considered given their potential benefit in older adults with CKD.
- Provision of standardised clinical pharmacy service using rigorous techniques by applying tools developed for use in older adults.
- Optimisation of medication regimens to manage kidney disease-related symptoms and burden, with the ultimate goal of improving HRQOL.
- The use of medication regimen complexity in lieu of, or in addition to, comorbidity to target high-risk patients in settings with limited clinical information, such as community pharmacies or when performing Home Medicines Reviews.

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APPENDICES

Appendix A. Electronic search strategy for systematic review (Chapter Two)

Pubmed/Medline: (((dose) OR dose adjustment)) AND ((renal* impair*) OR renal* insuffic*)

MESH terms: Renal insufficiency, chronic kidney disease, renal impairment

Embase: 'dose'/exp OR dose AND ('kidney'/exp OR kidney) AND ('disease'/exp OR disease) AND practice AND guideline AND ('human'/de OR 'practice guideline'/de) AND ('cohort analysis'/de OR 'controlled clinical trial'/de OR 'drug dose comparison'/de OR 'meta-analysis'/de OR 'outcomes research'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'systematic review'/de)

Emtree terms: Drug dose, Kidney failure

CINAHL: Renal* impair* OR renal* insuffic* AND Dose OR Dose adjustment

Cochrane Library: Renal impairment/ Renal insufficiency AND Dose OR Dose adjustment

PsychINFO: Renal insufficiency OR Renal impairment AND Dose OR Dose adjustment

Web of Science: Renal impairment AND Dose adjustment

OVID: Dose OR dose adjustment AND kidney disease OR renal impairment OR renal insufficiency

International Pharmaceutical Abstracts (IPA): (all(Dose) OR all (dose adjustment)) AND (all (renal impairment) OR all (kidney disease) OR all (renal insufficiency)) AND (all(pharmacist) OR all(pharmacy) OR all (pharmaceutical care))

Appendix B. Quality and risk of bias assessment used in the systematic review (Chapter Two)

Appendix B1. An adapted appraisal checklist according to Joanna Briggs Institute (JBI) meta-analysis of statistics assessment and review instrument

Experimental Studies (e.g. randomised/quasi-randomised, pre-post studies)	
1. Is the assignment of intervention groups truly random?	☐ Y ☐ N ☐ U ☐ NA
2. Are participants blinded to allocation of intervention?	☐ Y ☐ N ☐ U ☐ NA
3. Is allocation of treatment groups concealed from the investigator?	☐ Y ☐ N ☐ U ☐ NA
4. Are outcomes of people who withdrew described and included in the analysis?	☐ Y ☐ N ☐ U ☐ NA
5. Are those assessing the outcomes blind to the allocation of intervention?	☐ Y ☐ N ☐ U ☐ NA
6. Are the control and intervention groups comparable at entry?	☐ Y ☐ N ☐ U ☐ NA
7. Are groups treated identically other than for the named intervention?	☐ Y ☐ N ☐ U ☐ NA
8. Are outcome measured in the same way for all groups?	☐ Y ☐ N ☐ U ☐ NA
9. Are outcomes measured in a reliable way?	☐ Y

	☐	N
	☐	U
	☐	NA
10. Is appropriate statistical analysis used? Note: To score a "Y," the studies must compare the control Vs intervention groups (e.g., 2-sample *t* test, Fischer test), and a multivariable regression must have been applied to rule out confounders.	☐	Y
	☐	N
	☐	U
	☐	NA
Cohort (with control)/Case-controlled studies		
1. Is the sample representative of patients in the population? Note: Answer ''Y'' if the finding can be extrapolated to patients with similar stages and types of renal impairment	☐	Y
	☐	N
	☐	U
	☐	NA
2. Are the patients at a similar point in the course of their condition/illness?	☐	Y
	☐	N
	☐	U
	☐	NA
3. Has bias been minimised in relation to selection of cases and controls?	☐	Y
	☐	N
	☐	U
	☐	NA
4. Are confounding factors identified and strategies to deal with them stated? Note: To score a "Y," confounding factors for inappropriate prescribing must have been identified and controlled using multivariate analysis (e.g., logistic regression).	☐	Y
	☐	N
	☐	U
	☐	NA
5. Are outcome assessed using objective criteria?	☐	Y
	☐	N
	☐	U
	☐	NA
6. Is follow-up carried out over a sufficient period?	☐	Y
	☐	N
	☐	U
	☐	NA
7. Are the outcomes of people who withdrew described and included in the analysis?	☐	Y
	☐	N
	☐	U
	☐	NA
8. Are outcomes measured in a reliable way?	☐	Y
	☐	N

	☐ U ☐ NA
9. Is appropriate statistical analysis used? Note: To score a "Y," multivariate analyses (e.g., logistic regression) must have been applied.	☐ Y ☐ N ☐ U ☐ NA
Descriptive/Case series studies	
1. Is the study representative of patients with RI prescribed with medications affected by the renal system? Note: To score a "Y," the sampling should be random or pseudo-random, patients were representative, or the demographics of those included and excluded reported, and were comparable.	☐ Y ☐ N ☐ U ☐ NA
2. Were the criteria for inclusion in the sample clearly defined?	☐ Y ☐ N ☐ U ☐ NA
3. Were the confounding factors identified and strategies to rule them out stated? Note: To score a "Y," confounding factors for inappropriate prescribing must have been identified and controlled using multivariate analysis (e.g., logistic regression).	☐ Y ☐ N ☐ U ☐ NA
4. Were outcomes assessed using objective criteria	☐ Y ☐ N ☐ U ☐ NA
5. If comparisons are being made, were there sufficient descriptions of the groups	☐ Y ☐ N ☐ U ☐ NA
6. Was follow-up carried out over a sufficient period?	☐ Y ☐ N ☐ U ☐ NA
7. Were the outcomes of people who withdrew described and included in the analysis?	☐ Y ☐ N ☐ U ☐ NA
8. Were outcomes measured in a reliable way?	☐ Y ☐ N

Note: To score a "Y," objective criteria (e.g. the use of guidelines) must be applied by a trained data collector or studies investigators	☐ ☐	U NA
9. Was appropriate statistical analysis used? Note: To score a "Y," multivariate analyses (e.g., logistic regression) must have been applied.	☐ ☐ ☐ ☐	Y N U NA

Appendix B2. Quality assessment of the studies included in the systematic review based on the adapted version of Joanna Briggs Institute

Experimental Studies (e.g. randomised/quasi-randomised, pre-post studies)											
	1	2	3	4	5	6	7	8	9	10	Total Quality Score (Out of 10)
Awdishu et al, 2015	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Bhardwaja et al, 2009	Y	Y	Y	N	Y	Y	Y	Y	N	N	7
Erler et al, 2012	Y	Y	N	Y	N	Y	Y	Y	Y	N	7
Field et al., 2009	Y	Y	Y	N	N	Y	Y	Y	Y	N	6
Terrel et al, 2010	Y	Y	Y	N	Y	Y	Y	Y	Y	N	8
Cohort (with control)/Case-controlled studies											
	1	2	3	4	5	6	7	8	9		Total Quality Score (Out of 9)
Baum et al, 2010	Y	Y	Y	N	Y	Y	N	Y	N		6
Bertsche et al., 2009	Y	Y	NA	N	Y	NA	N	Y	Y		5
Cabello-Muriel et al, 2014	Y	Y	Y	N	Y	NA	NA	Y	N		5
Chertow et al, 2001	Y	Y	N	Y	Y	NA	NA	Y	Y		6
Falconnier et al, 2001	Y	Y	Y	N	Y	Y	N	Y	N		6
Hassen et al, 2009	Y	Y	Y	N	Y	NA	NA	Y	N		5
Holm et al, 2015	Y	Y	NA	N	Y	NA	NA	Y	Y		5
Nash et al, 2005	Y	Y	NA	U	Y	NA	NA	Y	Y		5
Pourrat et al, 2015	Y	Y	NA	N	Y	NA	NA	Y	Y		5
Quartarlo et al, 2007	Y	Y	Y	N	Y	NA	NA	Y	Y		6
Sellier et al, 2009	Y	Y	Y	Y	Y	NA	NA	Y	Y		7
Such Diaz et al., 2013	Y	Y	NA	N	Y	NA	NA	Y	Y		5
Via-Sosa et al 2013	Y	Y	Y	Y	Y	NA	NA	Y	N		6
Descriptive/Case series studies											
	1	2	3	4	5	6	7	8	9		Total Quality Score (Out of 9)
Alahdal et al, 2011	Y	Y	N	Y	NA	NA	NA	U	N		3
Bilge et al, 2013	Y	Y	N	Y	NA	NA	NA	Y	N		4
Blix et al, 2006	Y	Y	N	Y	Y	NA	NA	Y	N		5
Breton et al, 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y		9

Cantu et al, 1992	Y	Y	Y	Y	NA	NA	NA	U	Y	5
Chang et al, 2015	Y	Y	Y	Y	Y	NA	NA	Y	Y	7
Decloedt et al, 2010	N	Y	N	Y	NA	NA	NA	Y	N	3
Doody et al, 2015	Y	Y	Y	Y	NA	NA	NA	Y	Y	6
Drenth-van et al, 2015	Y	Y	Y	Y	NA	NA	NA	Y	N	5
Durand et al, 2013	N	Y	N	Y	NA	NA	NA	Y	N	3
Fahimi et al, 2012	N	Y	N	Y	NA	NA	NA	Y	N	3
Farag et al, 2014	Y	Y	Y	Y	NA	NA	NA	Y	Y	6
Getachew et al, 2015	N	Y	Y	Y	NA	NA	NA	Y	Y	5
Gheewala et al, 2014	Y	Y	N	Y	NA	NA	NA	Y	N	4
Jones et al, 2013	Y	Y	N	Y	NA	NA	NA	Y	N	4
Joosten et al, 2013	Y	Y	N	Y	NA	NA	NA	Y	N	4
Khanal et al, 2015	Y	Y	Y	Y	NA	NA	NA	Y	Y	6
Markota et al, 2009	N	Y	N	Y	Y	NA	NA	Y	N	4
Nielsen et al, 2014	N	Y	Y	Y	Y	NA	NA	Y	N	5
PapaioanNu et al, 2000	Y	Y	Y	Y	NA	NA	NA	Y	Y	6
Pillans et al, 2003	N	Y	N	Y	NA	NA	NA	Y	N	3
Prajapati et al, 2013	Y	Y	N	Y	NA	NA	NA	Y	N	4
Roberts et al, 2010	Y	Y	N	Y	Y	Y	NA	Y	N	6
Sah et al, 2014	N	Y	N	Y	NA	NA	NA	Y	N	3
Salomon et al, 2003	Y	Y	N	Y	NA	NA	NA	Y	N	4
Sheen et al, 2008	Y	Y	N	Y	NA	NA	NA	Y	Y	5
Sweileh et al, 2007	Y	Y	Y	Y	NA	NA	NA	U	Y	5
Van et al, 2006	Y	Y	Y	Y	Y	NA	NA	Y	N	6
Van et al, 2006 (letter)	Y	Y	Y	Y	Y	NA	NA	Y	N	6
Yap et al, 2005	N	Y	Y	Y	NA	NA	NA	Y	Y	5

Appendix C. Additional patient (laboratory and clinical) information by readmission status (supplementary to results in Chapter Four)

		30-day readmission			**90-day readmission**		
Characteristics	Total (n=204)	Yes (n=50)	No (n=154)	P	Yes (n=81)	No (n=123)	P
Hemoglobin (g/L), median (IQR)	118 (106-134)	117 (103-133)	118 (108-134)	0.54	118 (105-131)	119 (106-135)	0.68
Serum albumin (g/L), median (IQR)	32 (29-36)	32 (29-37)	32 (29-36)	0.66	33 (29-37)	32 (29-37)	0.34
Elevated Ca (>2.55 mmol/L), n (%)	24 (11.2)	5 (10)	44 (28)	**0.01**	6 (7.4)	18 (14.6)	0.12
Elevated PO_4 (>1.50 mmol/L), n (%)	15 (18.5)	4 (8)	11 (7)	0.84	8 (10)	7 (5.7)	0.26
Sodium (mmol/L), median (IQR)	142 (137-144)	140 (136-142)	139 (137-142)	0.42	142 (140-142)	139 (137-142)	0.92
Potassium (mmol/L), median (IQR)	5.2 (4.6-5.6)	4.7 (4.2-5.2)	4.6 (4.2-5.2)	0.95	4.6 (4.2-5.1)	4.6 (4.2-5.2)	0.59
ALT (IU/L), median (IQR)	16.5 (11-26)	19.5 (12-30)	16 (11-26)	0.11	16 (12-26)	17 (11-27)	0.56
ALP (IU/L), median (IQR)	88.5 (72-114)	92.5 (67-125)	88 (73-111)	0.44	89 (68-117)	88 (74-113)	0.82
AST (IU/L), median (IQR)	23 (16-52)	23 (16-35)	23 (15-32)	0.47	22 (16-30)	23 (16-33)	0.60
Common comorbidities, n (%)							
Hypertension,	145 (71)	30 (60)	115 (75)	0.05	55 (68)	90 (73)	0.42
Diabetes	70 (34)	22 (44)	48 (31)	0.10	30 (37)	40 (32.5)	0.51
Atrial fibrillation	66 (32)	16 (32)	50 (32)	0.95	25 (31)	41 (33)	0.71
Heart failure	49 (24)	11 (22)	38 (25)	0.70	20 (25)	29 (24)	0.85
Length of hospitalisation, median (IQR)	4 (2-8)	4 (2-8)	4 (3-8)	0.85	4 (2-8)	4 (3-8)	0.89
Primary cause of hospitalisation, n (%) Cardiovascular Infection Other	 80 (39.2) 25 (12.2) 99 (48.5)	 22 (44) 6 (12) 22 (44)	 58 (38) 19 (12) 77 (50)	0.71	 35 (43) 9 (11) 37 (46)	 45 (37) 16 (13) 62 (50)	0.63

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Appendix D. Changes in different kidney-disease targeted and generic (SF-36) health-related quality of life over time (supplementary to results in Chapter Six)

HRQOL scales	All participants (n=101)	Participants with follow-up data		
Kidney disease-related scales (n=63)		Baseline	Follow-up	*p-value**
Burden of kidney disease	75 (24)	77 (25)	70 (31)	**0.01**
Symptoms	79 (16)	78 (16)	77 (15)	0.59
Cognitive function	81 (16)	81 (15)	79 (16)	0.45
Effect of kidney disease	88 (13)	88 (14)	86 (17)	0.19
Sleep	64 (19)	62 (20)	62 (22)	0.80
Social interaction	82 (15)	82 (15)	82 (15)	0.89
Social support	83 (25)	87 (22)	82 (27)	0.18
Work status	43 (34)	42 (33)	41 (35)	0.64
Overall health status	63 (18)	62 (19)	59 (19)	0.08
SF-36 scales (n=60)				
Physical function	56 (26)	56 (26)	55 (30)	0.78
Physical role limitations	47 (42)	49 (39)	36 (38)	**0.01**
Pain	60 (28)	64 (27)	60 (28)	0.13
General health	49 (29)	46 (20)	44 (21)	0.29
Emotional well-being	79 (22)	77 (18)	76 (19)	0.57
Emotional role limitations	70 (40)	77 (36)	65 (38)	**0.02**
Social function	77 (30)	77 (26)	68 (29)	**0.004**
Vitality	55 (27)	48 (23)	45 (24)	0.22
SF36-PCS	38 (10)	38 (11)	37 (11)	0.22
SF36-MCS	51 (11)	52 (11)	49 (11)	**0.03**

Abbreviations: SF-36, 36-item short form survey; MCS, mental component summary; PCS, physical component summary
*Paired t-test
Results are in mean (SD)

Appendix E. Morisky-Green-Levine Medication Adherence Scale (Morisky et al., 1986)

It has indicated that you are taking medication for your health problems. Individuals have identified several issues regarding their medication-taking behaviour and we are interested in yours. There is no right and wrong answer. Please place a cross **(X)** in **ONE** box that best applies to you. Please answer the following questions based on your personal experience.

	Yes	No
1. Do you ever forget to take your medication?	☐	☐
2. Are you careless at times about taking your medication?	☐	☐
3. When you feel better, do you sometimes stop taking your medication?	☐	☐
4. Sometimes, if you feel worse when you take your medication, do you stop taking it?	☐	☐

Appendix F. Tool for Adherence Behaviour Screening (TABS) (George et al., 2006)

Many people find a way of using medicines that suits them. Here are some ways in which people have said they use their medicines. For each statement, please place a cross **(X)** in **ONE** box that best applies to you.

		Never	Rarely	Sometimes	Often	Always
1.	I get confused about my medication	☐	☐	☐	☐	☐
2.	I have strict routines for using my regular medication	☐	☐	☐	☐	☐
3.	I keep my medications close to where I need to use them	☐	☐	☐	☐	☐
4.	I ensure I have enough medication so that I don't run out	☐	☐	☐	☐	☐
5.	I strive to follow the instructions of my doctors	☐	☐	☐	☐	☐
6.	I make changes in the recommended management to suit my lifestyle	☐	☐	☐	☐	☐
7.	I vary my recommended management based on how I am feeling	☐	☐	☐	☐	☐
8.	I put up with my medical problems before taking any action	☐	☐	☐	☐	☐

Always = 5; Often = 4; Sometimes = 3; Rarely = 2; Never = 1

Appendix G. Perceived Burden of Medication (Neri et al., 2011)

This scale assesses to what extent you feel bothered by the medications you have to take, with "1" indicating, "Not at all bothered" and "5," "Extremely bothered." Please place a cross **(X)** in **ONE** box that best applies to you.

	1	2	3	4	5
1. Do you feel bothered by the number of medication(s) prescribed?	☐	☐	☐	☐	☐
2. Do you feel bothered by the size of the pill(s)?	☐	☐	☐	☐	☐
3. Do you feel bothered by the adverse effects of medication?	☐	☐	☐	☐	☐
4. Do you feel bothered by the number of times therapy should be administered during the day?	☐	☐	☐	☐	☐
5. Do you feel bothered by the need to take medicine(s) at work or in social contexts?	☐	☐	☐	☐	☐
6. Do you feel bothered by the need to drink in order to take medication(s)?	☐	☐	☐	☐	☐

1 = Not at all bothered; 2 = somewhat bothered; 3 = moderately bothered; 4 = Very bothered; 5 = extremely bothered

Appendix H. Medication Regimen Complexity Index (George et al., 2004)

MEDICATION REGIMEN COMPLEXITY INDEX

Patient ID: ----------
Total no. of medications (including prn/sos medications): ----------

Instructions

1. MRCI applies only to prescribed medications. All entries are to be made only based on information on the label or drug chart (at the time of dispensing or discharge). No assumptions are to be made based on clinical judgement.
2. There are three sections in the scale. Complete each section before proceeding to the next. At the end, add the scores for the three sections to give the MRCI.
3. If the same medication (same brand and same dosage form) is present more than once in different strengths in a regimen (e.g. Marevan 5mg, 3mg and 1 mg mdu), it is still considered as one medication.
4. In cases where the dosage is optional, choose the dosing instruction with the smallest dose/frequency. (e.g. Ventolin MDI 1-2 puffs, 2-3 times daily will get weightings for 'metered dose inhalers', 'variable dose' and 'twice daily'; but not for 'multiple units at one time')
5. In certain cases the dosing frequency needs to be calculated (e.g. Ranitidine 1mane and 1nocte is 1twice daily)
6. It is possible that with certain 'use as directed' instructions, the regimen will not get a score under dosing frequency (e.g. Prednisolone 5mg mdu)
7. If there is more than one dosing frequency direction, they should be scored for all the dosing frequency directions (e.g. Ventolin MDI 2 puffs bd and prn, will get scores for 'metered dose inhalers', 'multiple units at one time', 'twice daily' as well as 'prn')
8. Instances where two or more medications are mutually exclusive, they need to be scored twice or more as prn with the recommended dosing frequency (e.g. Ventolin MDI or Ventolin nebuliser twice daily will get scores for both 'metered dose inhalers' and 'nebuliser' under dosage forms, but needs to be scored two times for 'twice daily prn')
9. In cases where there is no matching option, choose the closest option (e.g. six times daily could be considered as 'q4h')

A) Circle the weighting corresponding to each dosage form (ONCE ONLY) present in the regimen.

Dosage Forms		Weighting
ORAL	Capsules/Tablets	1
	Gargles/Mouthwashes	2
	Gums/Lozenges	2
	Liquids	2
	Powders/Granules	2
	Sublingual sprays/tabs	2
TOPICAL	Creams/Gels/Ointments	2
	Dressings	3
	Paints/Solutions	2
	Pastes	3
	Patches	2
	Sprays	1
EAR, EYE & NOSE	Ear drops/creams/ointments	3
	Eye drops	3
	Eye gels/ointments	3
	Nasal drops/cream/ointment	3
	Nasal spray	2
INHALATION	Accuhalers	3
	Aerolizers	3
	Metered dose inhalers	4
	Nebuliser	5
	Oxygen/Concentrator	3
	Turbuhalers	3
	Other DPIs	3
OTHERS	Dialysate	5
	Enemas	2
	Injections: Prefilled	3
	Ampoules/Vials	4
	Pessaries	3
	Patient controlled analgesia	2
	Suppositories	2
	Vaginal creams	2
	Total for Section A	

B) For each medication in the regimen tick a box [√] corresponding to the dosing frequency. Then, add the no. of [√] in each category and multiply by the assigned weighting. In cases where there is no exact option, choose the best option.

Dosing Frequency	Medications	Total	Weighting	Weighting × No. of medications
Once daily			1	
Once daily prn			0.5	
Twice daily			2	
Twice daily prn			1	
Three times daily			3	
Three times daily prn			1.5	
Four times daily			4	
Four times daily prn			2	
q 12h			2.5	
q 12h prn			1.5	
q 8h			3.5	
q 8h prn			2	
q 6h			4.5	
q 6h prn			2.5	
q 4h			6.5	
q 4h prn			3.5	
q 2h			12.5	
q 2h prn			6.5	
prn/sos			0.5	
On alternate days or less frequently			2	
Oxygen prn			1	
Oxygen <15hrs			2	
Oxygen >15hrs			3	
			Total for Section B	

C) Tick a box [√] corresponding to the additional directions, if present in the regimen. Then, add the no. of [√] in each category and multiply by the assigned weighting.

Additional Directions	Medications	Total	Weighting	Weighting × No. of medications
Break or crush tablet			1	
Dissolve tablet/powder			1	
Multiple units at one time (e.g. 2 tabs, 2 puffs)			1	
Variable dose (e.g. 1-2 caps, 2-3 puffs)			1	
Take/use at specified time/s (e.g. mane, nocte, 8 AM)			1	
Relation to food (e.g. pc, ac, with food)			1	
Take with specific fluid			1	
Take/use as directed			2	
Tapering/increasing dose			2	
Alternating dose (e.g. one mane & two nocte, one/ two on alternate days)			2	
			Total for Section C	

Medication Regimen Complexity = Total (A) + Total (B) + Total (C)=

Appendix I. Medication Appropriateness Index (Hanlon et al., 1992)

Patient ID# _____ Evaluator _____Date_____

Drug Code _____
Drug_____

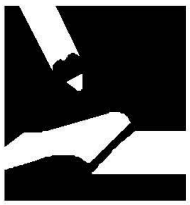
To assess the appropriateness of the drug, please answer the following questions and circle the applicable score:				
1. Is there an indication for the drug? Comments:	1 Indicated	2	3 Not Indicated	9 DK†
2. Is the medication effective for the condition? Comments:	1 Effective	2	3 Ineffective	9 DK
3. Is the dosage correct? Comments:	1 Correct	2	3 Incorrect	9 DK
4. Are the directions correct? Comments:	1 Correct	2	3 Incorrect	9 DK
5. Are the directions practical? Comments:	1 Practical	2	3 Impractical	9 DK
6. Are there clinically significant drug–drug interactions? Comments:	1 Insignificant	2	3 Significant	9 DK
7. Are there clinically significant drug–disease/condition interactions? Comments:	1 Insignificant	2	3 Significant	9 DK
8. Is there unnecessary duplication with other drug(s)? Comments:	1 Necessary	2	3 Unnecessary	9 DK
9. Is the duration of therapy acceptable? Comments:	1 Acceptable	2	3 Unacceptable	9 DK
10. Is this drug the least expensive alternative compared to others of equal utility? Comments:	1 Least expensive	2	3 Most expensive	9 DK

Appendix J. Kidney Disease and Quality of Life Short Form (KDQOL-SF™ 1.3)

Your Health
– and –
Well-Being

Kidney Disease and Quality of Life (KDQOL-SF™ 1.3)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.



Thank you for completing these questions!

Study of Quality of Life For Patients on Dialysis

What is the purpose of the study?

This study is being carried out in cooperation with physicians and their patients. The purpose is to assess the quality of life of patients with kidney disease.

What will I be asked to do?

For this study, we want you to complete a survey today about your health, how you feel and your background.

Confidentiality of information?

We do not ask for your name. Your answers will be combined with those of other participants in reporting the findings of the study. Any information that would permit identification of you will be regarded as strictly confidential. In addition, all information collected will be used only for purposes of the study, and will not be disclosed or released for any other purpose without your prior consent.

How will participation benefit me?

The information you provide will tell us how you feel about your care and further understanding about the effects of medical care on the health of patients. This information will help to evaluate the care delivered.

Do I have to take part?

You do not have to fill out the survey and you can refuse to answer any question. Your decision to participate will not affect your opportunity to receive care.

Your Health

This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.

1. **In general, would you say your health is: [Mark an ☒ in the one box that best describes your answer.]**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Page 1

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark an ☒ in a box on each line.]

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than one kilometer	☐ 1	☐ 2	☐ 3
h	Walking several blocks	☐ 1	☐ 2	☐ 3
i	Walking one block	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		Yes	No
a	Cut down the amount of time you spent on work or other activities	☐ 1	☐ 2
b	Accomplished less than you would like	☐ 1	☐ 2
c	Were limited in the kind of work or other activities	☐ 1	☐ 2
d	Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

		Yes	No
a	Cut down the amount of time you spent on work or other activities	☐ 1	☐ 2
b	Accomplished less than you would like	☐ 1	☐ 2
c	Didn't do work or other activities as carefully as usual	☐ 1	☐ 2

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6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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The next three questions are personal and relate to your sexual activity, but your answers are important in understanding how kidney disease impacts on people's lives.

16. Have you had any sexual activity in the <u>past 4 weeks</u>?

(Circle One Number)

No .....1 → If no, please skip to Question 17

Yes 2

How much of a problem was each of the following in the <u>past 4 weeks</u>?

	Not a problem	A little problem	Somewhat of a problem	Very much a problem	Severe problem
a Enjoying sex?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Becoming sexually aroused?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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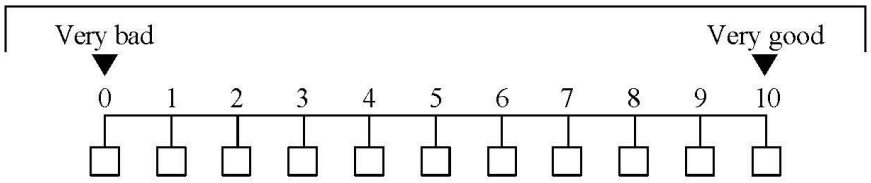
17. For the following question, please rate your sleep using a scale ranging from 0 representing "very bad" to 10 representing "very good."

If you think your sleep is half-way between "very bad" and "very good," please mark the box under the number 5. If you think you sleep is one level better than 5, mark the box under 6. If you think your sleep is one level worse than 5, mark the box under 4 (and so on).

On a scale from 0 to 10, how would you rate your sleep overall? [Mark an ☒ in one box.]



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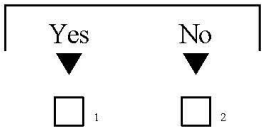
18. How often during the <u>past 4 weeks</u> did you...

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
a Awaken during the night and have trouble falling asleep again?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b Get the amount of sleep you need?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c Have trouble staying awake during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

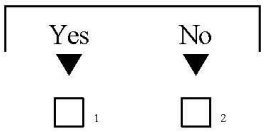
19. Concerning your <u>family and friends</u>, how satisfied are you with...

	Very dissatisfied	Somewhat dissatisfied	Somewhat satisfied	Very satisfied
a The amount of time you are able to spend with your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4
b The support you receive from your family and friends?	☐ 1	☐ 2	☐ 3	☐ 4

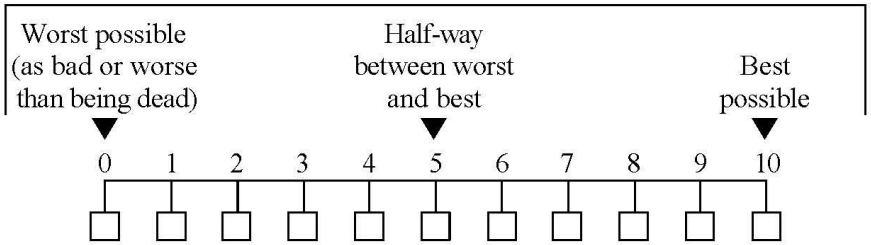
20. During the <u>past 4 weeks</u>, did you work at a paying job?



21. Does your health keep you from working at a paying job?



22. Overall, how would you rate your health?



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Satisfaction With Care

23. Think about the care you receive for kidney dialysis. In terms of your satisfaction, how would you rate the friendliness and interest shown in you as a person?

Very poor	Poor	Fair	Good	Very good	Excellent	The Best
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

24. How <u>true</u> or <u>false</u> is each of the following statements?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a Dialysis staff encourage me to be as independent as possible	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Dialysis staff support me in coping with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a Did you feel full of pep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b Have you been a very nervous person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f Have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
h Have you been a happy person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

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10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. Please choose the answer that best describes how <u>true</u> or <u>false</u> each of the following statements is for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Your Kidney Disease

12. How true or false is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a My kidney disease interferes too much with my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Too much of my time is spent dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I feel frustrated dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d I feel like a burden on my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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13. These questions are about how you feel and how things have been going during the <u>past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the <u>past 4 weeks</u>…

	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
a Did you isolate yourself from people around you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
b Did you react slowly to things that were said or done?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
c Did you act irritable toward those around you?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
d Did you have difficulty concentrating or thinking?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
e Did you get along well with other people?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
f Did you become confused?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

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14. During the <u>past 4 weeks</u>, to what extent were you bothered by each of the following?

		Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
		▼	▼	▼	▼	▼
a	Soreness in your muscles?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Chest pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Cramps?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Itchy skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	Dry skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f	Shortness of breath?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	Faintness or dizziness?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	Lack of appetite?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	Washed out or drained?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
j	Numbness in hands or feet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
k	Nausea or upset stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
l	(Hemodialysis patient only) Problems with your access site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
m	(Peritoneal dialysis patient only) Problems with your catheter site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Effects of Kidney Disease on Your Daily Life

15. Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease <u>bother</u> you in each of the following areas?

	Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
	▼	▼	▼	▼	▼
a. Fluid restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Dietary restriction?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Your ability to work around the house?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Your ability to travel?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Being dependent on doctors and other medical staff?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Stress or worries caused by kidney disease?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Your sex life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Your personal appearance?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Appendix K. Ethics Approvals

Appendix K1. Ethics approval for retrospective studies

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

04 January 2017

Dr Tabish Razi Zaidi
C/- Pharmacy

Sent via email

Dear Dr Razi Zaidi

REF NO: H0016044
TITLE: Retrospective evaluation of medication inappropriateness and treatment regimen complexity in patients with chronic kidney disease

Document	***Version***	***Date***
Low risk + waiver		
Privacy Form		

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **14 December 2016** to be conducted at the following site(s):

Royal Hobart Hospital
University of Tasmania

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing

from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.utas.edu.au/research-admin/research-integrity-and-ethics-unit-rieu/human-ethics/human-research-ethics-review-process/health-and-medical-hrec/managing-your-approved-project

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for four years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 14 December 2017. You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Jude Vienna-Hallam
Ethics Administration Officer
Office of Research Services
University of Tasmania
Private Bag 01
Hobart Tas 7001
(Building 1, Ground Floor, 301 Sandy Bay Road)
T +61 3 6226 2764

Please use your ethics reference number in all correspondence (H00xxxxx)

Appendix K2. Ethics amendment for the prospective study

Dear Dr McKercher

Ethics Ref: H0015099
Title: The psychosocial determinants of treatment pathways, clinical outcomes and costs in Tasmanians with advanced chronic kidney disease.

This email is to confirm that the following amendment was approved by the Chair of the Tasmania Health and Medical Human Research Ethics Committee on 19/9/2016:

Amendment to collect information on patient's medication history and addition of student and co-investigator Information Sheet and consent form revised received 20/05/16 Miscellaneous Questionnaire MMAS 8

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the National Statement on Ethical Conduct in Human Research (NHMRC 2007).

This email constitutes official approval. If your circumstances require a formal letter of amendment approval, please let us know.

Should you have any queries please do not hesitate to contact me.

Kind regards

Lauren Black

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